EVALUATION OF BOTULINUM TOXIN A AND GREATER OCCIPITAL NERVE BLOCK IN TREATMENT OF CHRONIC MIGRAINE

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Submitted By

DR. BALVEEN SINGH

DEPARTMENT OF NEUROLOGY
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA, PUNJAB

DECLARATION BY THE CANDIDATE

I hereby declare that the thesis entitled "**EVALUATION OF BOTULINUM TOXIN A AND GREATER OCCIPITAL NERVE BLOCK IN TREATMENT OF CHRONIC MIGRAINE**" submitted towards partial fulfillment of the requirements for the award of DM in Neurology degree to BFUHS is a compilation of original work carried out by me under the supervision of **Dr. Gagandeep SIngh**, Professor & Head, Department of Neurology, **Dr. Monika Singla**, Associate Professor, Department of Neurology. No part of this thesis has formed the basis for the award of any degree previously.

_____

DR. BALVEEN SINGH
Department of Neurology,
Dayanand Medical College & Hospital,
Ludhiana, Punjab

Date:

Place:

CERTIFICATE OF SUPERVISORS

This is to certify that the work incorporated in this thesis entitled "**EVALUATION OF BOTULINUM TOXIN A AND GREATER OCCIPITAL NERVE BLOCK IN TREATMENT OF CHRONIC MIGRAINE"** has been carried out by **Dr. Balveen Singh** under our direct supervision. The data incorporated in this thesis is original and genuine and has been carried out by the candidate himself.

Signature of Supervisor

Dr. Gagandeep Singh
Professor & Head
Department of Neurology
DMCH, Ludhiana

Signature of Co-Supervisor

Dr. Monika Singla
Associate Professor
Department of Neurology
DMCH, Ludhiana

Date:

ENDORSEMENT BY THE HEAD OF THE INSTITUTE

This is to certify that the thesis entitled "**EVALUATION OF BOTULINUM TOXIN A AND GREATER OCCIPITAL NERVE BLOCK IN TREATMENT OF CHRONIC MIGRAINE "** is a bonafide research work done by **Dr. Balveen Singh** under the supervision of **Dr. Gagandeep SIngh**, Professor & Head, Department of Neurology, **Dr. Monika Singla**, Associate Professor, Department of Neurology in this institution.

Principal

Dr. Sandeep Puri
Principal
DMC&H, Ludhiana

Date:

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Signature

Dr. Balveen Singh
Department of Neurology,
Dayanand Medical College & Hospital,
Ludhiana, Punjab - 141001

Date:

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"The brain is like a muscle. When it is in use, we feel very good. Understanding is joyous"

- Carl Sagan, American Astrophysicist

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Dr. Balveen Singh

LIST OF ABBREVIATIONS

AEs:	adverse events
BoNT-A:	Botulinum toxin type A
BOTOX:	Botulinum toxin type A
CGRP:	calcitonin gene-related peptide
CM:	Chronic migraine
CSF:	cerebrospinal fluid
FDA:	Food and drug administration
GABA:	gamma aminobutyric acid
GBD:	Global burden of disease
GON:	Greater occipital nerve
GONB:	Greater occipital nerve block
ICHD:	International classification of headache disorders
TGVS:	trigeminovascular system
tmax:	time to peak plasma level
VAS:	Visual analog scale
avg.-	Average
MCI-	mild cognitive impairment
min.-	minimum
MMSE-	Mini-Mental State Examination

ABSTRACT

Introduction: Migraine is a common disabling primary headache disorder. Chronic migraine, defined as headaches on ≥15 days per month for ≥3 months, of which ≥8 days meet criteria for migraine without aura or respond to migraine-specific treatment. It results in substantial disability and therefore the efficacy of Greater occipital nerve block and Botulinum toxin A in patients with adult chronic migraine needs to be studied in detail.

Aim: The aim of our study was to demonstrate safety and efficacy of administration of greater occipital nerve block and botulinum toxin A in patients with chronic migraine.

Methods: A non-randomized prospective observational study was conducted on adult patients with chronic migraine, patients were offered Botulinum toxin A or Greater Occipital Nerve block after discussion of all available treatment options. Patients were followed for 28 days and a headache diary was used to evaluate the frequency and intensity of headache in chronic migraine patients receiving any one of the two modalities. All follow up and new patient's presenting to DMCH Ludhiana from March 2020 to August 2021 were enrolled for study after taking informed and written consent.

Results: A total of 20 eligible patients consented to participate. Among the patients who received Botox Injection, all were females, and the mean age was 42.25 years. Patients had complained of 26 days of headache4 weeks prior while after the injection, it reduced to 12 headache days. The mean headache severity in terms of Visual Analog Scale also was decreased 4 weeks after the injection, the patients had 7 mean headache days with severity 0-4, while they had 3.75 mean headache days with severity 4-7 and only 1.5 mean headache days with severity 7-10.Among the patients who received GONB, the mean age was 42.13 years and 13 patients were female. Patients had an average number of 22.63 headache days prior to the injection in the last 4 weeks, while after the injection, it reduced to 10.81 mean headache days. The mean headache severity in terms of Visual Analog Scale also was decreased 4 weeks after the injection, the patients had 7.31 mean headache days with severity 0-4, they had 2.63 mean headache days with severity 4-7 and only 0.88 mean headache days with severity 7.No serious adverse events were reported in the both the groups, however a relatively few adverse effects were reported

Conclusions: Chronic migraine treatment with onabotulinum toxin-A and GONB was associated with a reduction in monthly headache days and decreased headache severity (according to VAS scale); the data support the safety and efficacy for the use of onabotulinum toxin-A for the treatment of chronic migraine in clinical practice.

Key words: Headache, Migraine, Chronic migraine, greater occipital nerve block, onabotulinum toxin type-A.

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Introduction

Chronic migraine (CM) is diagnosed when headaches occur on 15 days or more per month for at least 3 months out of which at least 8 days or more with headaches are associated with migraine. There is a marked reduction in performance of patients, quality of life, social activities and family, in addition to the work or school being affected. [1,2]

CM has a female preponderance and it occurs 2.5–6.5 times more often in women than in men[3,4] and is associated with significant individual disability which lead on to societal and economic burden. [5] People with CM face barriers in receiving the proper medical management of their disease.[6]

Less than 5% of people with CM were receiving appropriate care, which included consulting a healthcare professional, being accurately diagnosed, and being prescribed a treatment regimen.[7] This may be partially attributed to a lack of awareness of the general public to the available treatment options. CM is a complication of episodic migraine [8] affecting 2% of the general population, and is frequently associated with a secondary headache, medication overuse headache (MOH), which itself is as a co-morbidity as well as a marker of poor control of the migraine itself.[6,9]

Chronic migraine (CM) is the most severe form in the migraine pathology spectrum and its disabling effects are not only related to the physical health of patients but also reverberate on social and economic aspects. The available pharmacological treatments of CM are quite limited. Currently, people with CM are generally treated with antidepressants (amitriptyline), anticonvulsants (valproate, topiramate), beta blockers (propranolol, metoprolol, timolol, bisoprolol), and angiotensin II receptor 1A blockers (candesartan). [10, 11] Of these, only a few drug treatments like topiramate[12] and onabotulinum toxin-A[13] have an efficacy proven by randomized controlled trials.

Most drugs used in the treatment of CM have been investigated only by small open studies.[14] Management of CM patients is complicated by poor therapeutic adherence due to insufficient efficacy of drug therapies and their side effects.[15]

Since there are no predictors of treatment response available to date, preventive medications are selected by trial and error, taking into account the drug side effects, patient co-morbidities and the patient clinical profile, more so than by their efficacy differences. Each drug is recommended for at least 6 months before assessing inefficacy and CM patients try on average 3-4 therapeutic drugs with severe patient discomfort and frustration of the doctor. Most of patients interrupt treatment due to lack of efficacy or side effects and about 9% achieve clinical improvement.[16]Management of CM patients is further complicated by poor therapeutic adherence due to their side effects and insufficient efficacy of drug therapies.[15]

Primary headache patients, complain of pain affecting both the trigeminally innervated anterior regions of the head and the posterior region innervated by the C2 spinal root. This is due to the overlap of processing of nociceptive information at the level of the second order neurons since bothC1 to C2 spinal afferents and trigeminal afferents converge on the trigeminal nucleus caudalis and dorsal horn nuclei of the upper cervical spinal cord. [17-19] The greater occipital nerve (GON) is composed of sensory fibres which originate predominantly at C2 spinal level with cutaneous distribution covering the posterior head up to the vertex. GON block with corticosteroids and/or local anaesthetics agent has been employed for the acute [20] and prophylactic treatment of migraine [21], cluster headache [23] and cervicogenic headache[22] for more than 50 years.

The rationale of performing a GONB for the treatment of chronic headache states on the anatomical connections between trigeminal and upper cervical sensory fibres at the level of the trigeminal nucleus caudalis. [24, 25] However, the reason for the improvement of clinical

symptoms after occipital nerve block in primary headache patients is unknown. Several hypotheses have been suggested, which includes inhibition of central-pain processing mechanisms at the brainstem level, a systemic steroid effect and placebo effects.

Patients with migraine, when affected by chronic and aura subtype forms, have increased skin sensitivity to non-noxious stimuli and GONB play a role in cutaneous allodynia in migraine. Allodynia is thought to be caused by the headache and the activation of nociceptors with the development of central sensitization in subjects which have altered regulation of the central nociceptive pathway.[26] The persistence of pain sensation induces central sensitization in the caudal nucleus of the trigeminal nerve by lowering the neuronal pain threshold.[27]

GONB alleviates head pain by altering with the nociceptive input to the trigeminal-cervical complex. Experimental studies suggests electrical stimulation and local anaesthetic blocks of the GON have a facilitatory effect on dural nociceptive stimulation suggesting the subsequent induction of central sensitization on second-order neurone receiving cervical and trigeminal input.[28] A disturbance in and around the region of the head can provoke pain in the distribution of the upper cervical and trigeminal and nerves due to convergence of the afferent fibres of the three superior cervical roots on the neurones of the trigeminal nerve nucleus[29] so the analgesic action of GONB is most likely initiated by a diffuse inhibitory process.

Botulinum toxin type A (BoNTA) is a neuromuscular blocking agent which has a wide range of clinical applications that includes the treatment of various conditions characterized by autonomic dysfunction, muscle overactivity, or chronic pain. [30-32] Briefly, (ona)BoNTA is a purified neurotoxin complex which consists of neurotoxin botulinum toxin A and several accessory (non-neurotoxic) peptides. It is produced by fermentation of Hall strain Clostridium botulinum type A.[30] The potency of (ona)BoNTA is expressed in

biological units, where 1 unit of (ona)BoNTA is the estimated dose of intraperitoneally injected toxin lethal for 50% of the population of female Swiss Webster mice weighing 18–20 g.[33]

The mode of action of (ona)BoNTA – inhibition of neurotransmission – is well characterized; itexerts muscle relaxant (paralytic) and anhidrotic effects by blocking the release of acetylcholine from the presynaptic terminals of efferent neurones. [34-36] There is primarily preclinical evidence, that (ona)BoNTA exerts a direct antinociceptive (analgesic) effect, independent of its neuromuscular activity. [37-40]

It is hypothesized that the analgesic effect is mediated through inhibition of the release of neurotransmitters and neuro- peptides, such as substance P,glutamate and calcitonin gene-related protein, from peripheral and/or central nociceptive neurones, depending on whether (ona)BoNTA is administered centrallyor peripherally; reducing the release of these proinflammatory mediators may, suppress peripheral and/or central sensitization.[37-39] It has been suggested that peripherally administered (ona)BoNTA could indirectly counteract sensitization of muscle nociceptors through the inhibition of the release of pro-inflammatory mediators from overactive muscle fibres.[40] Sensitization of peripheral trigeminovascular nociceptive neurones has been implicated in the pathophysiology of migraine pain;[41,42] while not fully understood, the mechanism of action underlying the headache prophylaxis effect of intramuscularly administered (ona)BoNTA is thought to involve inhibition of peripheral (and thereby also central) sensitization in this afferent neuronal pathway.[43]

In summary, our current notion is that onabotulinumtoxinA exerts a prophylactic effect on CM via dual mechanism: (1) it inhibits the peripheral release of neurotransmitter and inflammatory neuropeptide-containing vesicles (e.g., glutamate, CGRP[44], substance P[39]), and (2) it interferes with cell surface expression of relevant peripheral nerve receptors and ion channels. In a patient with CM, on a botulinum toxin A is injected into the craniofacial–cervical region. Accordingly, in the

periphery, peripheral sensitization is disrupted, and central sensitization is indirectly blocked, which results in an antinociceptive response in the sensitized trigeminal nerve and cervical afferents.[37,38,44-46]

Aims and Objectives

The aim of our study was to demonstrate safety and efficacy of administration of greater occipital nerve block and botulinum toxin A in patients with chronic migraine.

Review of literature

HEADACHE

Headache affects almost everyone at some time in their life. Half of the world's adult population is estimated to have an active headache disorder[47].Headache is one of the most common reasons patients seek medical attention, being responsible for more disability than any other neurologic problem.

Diagnosis and management are based on careful clinical approach augmented through an understanding of the anatomy, physiology and pharmacology of the nervous system pathways mediating the various headache disorders.

A classification system developed by the International Headache Society(48) characterizes headache as primary or secondary. The primary headache disorders can be precipitated by secondary conditions but do not have any underlying structural cause.

Table 1 Headache Classification

THE PRIMARY HEADACHES

Migraine and its subtypes
Tension-type headache and its subtypes
Trigeminal autonomic cephalalgias
Cluster headache
Paroxysmal hemicranias
Short-lasting unilateral neuralgiform headache attacks
Hemicrania continua
Other primary headache disorders
Primary cough headache
Primary exercise headache
Primary headache associated with sexual activity
Primary thunderclap headache
Cold-stimulus headache
External-pressure headache
Primary stabbing headache
Nummular headache
Hypnic headache
New daily persistent headache

THE SECONDARY HEADACHES

Headache attributed to trauma or injury to the head and/or neck Headache attributed to cranial or cervical vascular disorder Headache attributed to nonvascular intracranial disorder Headache attributed to a substance or its withdrawal

Headache attributed to infection
Headache attributed to disorder of homeostasis
Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure
Headache attributed to psychiatric disorder

PAINFUL CRANIAL NEUROPATHIES, OTHER FACIAL PAINS, AND OTHER HEADACHES

Painful cranial neuropathies and other facial pains
Other headache disorders

From The International Classification of Headache Disorders[48]

ANATOMY AND PHYSIOLOGY OF HEADACHE

Peripheral nociceptors stimulation in response to either tissue injury, visceral distension, or any other factors causes pain, the perception of pain is a normal physiologic response mediated by a healthy nervous system. Pain can also result when pain producing pathways of the central or peripheral nervous system are damaged or activated inappropriately. Headache may originate from either or both mechanisms[49].

The structures involved in primary headache are the following[50]:

- The large intracranial vessels and the dura matter, falx cerebri and the peripheral terminals of trigeminal nerve innervating these structures
- The caudal portion of the trigeminal nucleus, that extends into the dorsal horns of the upper cervical spinal cord and receives input from the first and second cervical nerve roots known as" The trigemino-cervical complex"
- Rostral pain-processing regions, such as ventro-postero-medial thalamus and the cortex
- The pain-modulatory systems in the brain that modulates input from trigeminal nociceptors at all levels of the pain-processing pathways and influence vegetative functions, such as brainstem and hypothalamus structures.

The trigemino-vascular system consists of innervation of large intracranial vessels and dura matter by the trigeminal nerve. Cranial autonomic symptoms, such as conjunctival injection, lacrimation, nasal congestion, peri-orbital swelling, rhinorrhoea, aural fullness, and ptosis, are prominent in the trigeminal autonomic cephalalgias, including cluster headache and paroxysmal hemicrania, and are also seen in migraine. The activation of cranial parasympathetic pathways, and functional imaging studies suggest that vascular changes in migraine and cluster headache, are driven by these cranial autonomic systems.

Migraine and other primary headache types are not —vascular headaches; they do not reliably manifest vascular changes, and treatment outcomes cannot be predicted by vascular effects. Migraine is a brain disorder and is best understood and managed as such.

PRIMARY HEADACHE DISORDERS

Primary headaches are disorders in which headache and its associated features occur in the absence of any exogenous cause. The most common types are migraine, tension-type headache, and the trigeminal autonomic cephalalgias[49].

In 1988, the Headache Classification Committee of the International Headache Society introduced a detailed classification of headaches. This has been subsequently revised, by the International Classification of Headache Disorders (**Headache Classification Committee, 2013)**[48]. Its four main parts include: 1) primary headaches, 2) secondary headaches, 3) painful cranial neuropathies, other facial pains and other headaches, and 4) appendix*.

* The purpose of the appendix in the ICHD-3 is to present research criteria for multiple entities that are not sufficiently validated.

Table 2 Classification of Headache Disorders[48]

PART ONE: THE PRIMARY HEADACHES

1. Migraine

2. Tension-type headache

3. Trigeminal autonomic cephalalgias

4. Other primary headache disorders

PART TWO: THE SECONDARY HEADACHES

5.Headache attributed to trauma or injury to the head and/or neck

6. Headache attributed to cranial or cervical vascular disorder

7. Headache attributed to nonvascular intracranial disorder

8. Headache attributed to a substance or its withdrawal

9. Headache attributed to infection

10.Headache attributed to disorder of homeostasis

11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure

12. Headache attributed to psychiatric disorder

PART THREE: PAINFUL CRANIAL NEUROPATHIES, OTHER FACIAL PAINS AND OTHER HEADACHES

13. Painful cranial neuropathies and other facial pains
14. Other headache disorders

APPENDIX

From Headache Classification Committee of the International Headache Society, 2013[48]

MIGRAINE

Definition

The term *migraine is* derived from the ancient Greek word, *hemikranios*, (means "half head") underscoring the unilateral distribution of pain that is present in about 60%–75% of people with migraine [51,52].

The four phases of migrainous attack are: premonitory phase, aura, headache phase, and postdrome. In addition to head pain, the "headache phase" consists of a combination of photosensitivity, phonosensitivity, cutaneous allodynia, olfactory hypersensitivity, nausea and vomiting.

Migraine is a disabling primary headache disorder. Many epidemiological studies have documented its high prevalence and socio-economic and personal impacts. It was ranked as the third most prevalent disorder in the world in the Global Burden of Disease Study2010 (GBD2010). In GBD2015, it was ranked as the third–highest cause of disability worldwide in both males and females under the age of 50 years[48].

Migraine can be recognized by its activators, referred to as triggers. The brain of the migraineur is sensitive to environmental and sensory stimuli [53]; migraine-prone patients find it difficult habituate easily to sensory stimuli. This sensitivity is increased in females during the menstrual cycle. Headache can be initiated or amplified by various triggers[54-56], including bright lights, glare, sounds, or other afferent stimulation; stormy weather; hunger[57]; physical exertion; or barometric pressure changes; hormonal fluctuations during menses; lack of or excess sleep; and alcohol. Knowledge of a patient's susceptibility to specific triggers is useful in management strategies involving lifestyle adjustments.

Chronic migraine (CM) is defined as headache on 15 days or more per month for at least 3 months of which at least 8 days or more with headaches are associated with migraine. There is severe reduction in performance of patients, quality of life, family and social activities, in addition to the work or school being affected.

CLASSIFICATION [48]

Migraine has two major types: 1.1 Migraine without aura is characterized by headache with specific features and associated symptoms; 1.2 Migraine with aura is characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Some patients experience a prodromal phase, occurring hours or days before the headache, and/or a post-dromal phase following headache resolution. Prodromal and post-dromal symptoms include hypoactivity, hyperactivity, depression, repetitive yawning, cravings for particular foods, fatigue and neck stiffness and/or pain. [48]

1. Migraine [48]

- **1.1 Migraine without aura**
- **1.2 Migraine with aura**
    - 1.2.1 Migraine with typical aura
        - 1.2.1.1 Typical aura with headache
        - 1.2.1.2 Typical aura without headache
    - 1.2.2 Migraine with brainstem aura
    - 1.2.3 Hemiplegic migraine
        - 1.2.3.1 Familial hemiplegic migraine (FHM)
            - 1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
            - 1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
            - 1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

            - 1.2.3.1.4 Familial hemiplegic migraine, other loci
        - 1.2.3.2 Sporadic hemiplegic migraine (SHM)
    - 1.2.4 Retinal migraine
- **1.3 Chronic migraine**
- **1.4 Complications of migraine**
    - 1.4.1 Status migrainosus
    - 1.4.2 Persistent aura without infarction
    - 1.4.3 Migrainous infarction
    - 1.4.4 Migraine aura-triggered seizure
- **1.5 Probable migraine**
    - 1.5.1 Probable migraine without aura
    - 1.5.2 Probable migraine with aura
- **1.6 Episodic syndromes that may be associated with migraine**
    - 1.6.1 Recurrent gastrointestinal disturbance
        - 1.6.1.1 Cyclical vomiting syndrome
        - 1.6.1.2 Abdominal migraine
    - 1.6.2 Benign paroxysmal vertigo
    - 1.6.3 Benign paroxysmal torticollis

PATHOPHYSIOLOGY

Role of the trigemino vascular system

The pathophysiology of migraine implicates the activation and sensitisation of the trigemino vascular system. (TGVS) (Figure 1)[58,59]. The TGVS comprises of the trigeminal ganglion (TG) projecting peripherally to cerebral blood vessels and dura mater which is innervated by the trigeminal nerve and centrally to the TCC in the brainstem and spinal cord. Peripheral nociceptive input comes from nociceptors and nociceptive A-δ and C fibres innervating the intracerebral blood vessels and dura mater[59]. Nociceptive input is then transmitted to trigeminal nerve and its ganglion, and synapses on second-order neurons in the TCC [60].

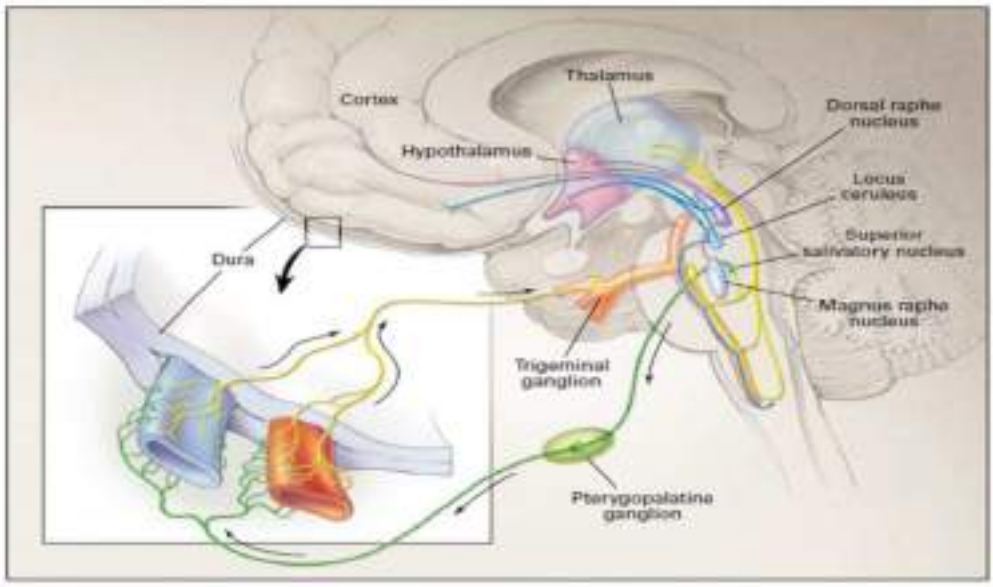


Figure 1.Pathophysiology of migraine.

The key pathways are the trigemino vascular input from the meningeal vessels, which passes through the trigeminal ganglion and then synapses on second-order neurons in the trigemino cervical complex. These neurons, then, decussates in the brainstem and form synapses with neurons in the thalamus [60].

Mechanisms responsible for headaches phases

The exact mechanisms responsible for the premonitory, aura, headache, and postdrome phases of headaches, and transitioning between these phases, remain unclear. Overlap between mechanisms of these phases is suggested in current evidence. In the premonitory phase, the central nervous system mediates the release of dopamine and blood flow in the hypothalamus increase [61]. Just before the aura phase, there is a decrease in regional cortical cerebral blood flow, usually starting posteriorly and then progressing anteriorly[48], the decrease in blood flow is above the threshold for ischemic injury. The decrease in blood flow progresses into increased blood flow over a period of hours and this regional cortical cerebral blood flow is believed to be due to cortical spreading depression (CSD), it is the electrophysiological substrate of the migraine aura. Cortical spreading depression starts in the occipital pole and further spreads forward over the cerebral hemisphere at a rate of about 2 to 4 mm/min. Secondary to cortical spreading depression wave. There is a corresponding initial phase of hyperaemia followed by oligemia. The cortical spreading depression wave is not confined within the distribution of any particular cerebral artery, but crosses the areas perfused by the middle and posterior cerebral arteries while advancing. The period of brain activation followed by brain deactivation might correspond with the pattern of “positive” symptoms (e.g., visual scintillations) followed by “negative” symptoms (e.g., visual scotoma) typical of the migraine aura. Functional MRI studies support the notion that cortical spreading depression is the underlying mechanism for migraine aura.

The headache phase of migraine involves sensitisation and activation of meningeal nociceptors and afferents by mechanical stimuli. The sensitisation of meningeal afferents provides a mechanism that explains the throbbing nature of the migraine headache as well as the exacerbation of the headache during events that increase intracranial pressure [58]. After the headache phase, symptoms occur which compromise the postdrome phase. Few studies about postdrome

phase suggest that it is linked with persistent changes in brain activity past the headache phase [62]. These changes include increased blood flow in the visual cortex, bilateral posterior cortical hypoperfusion, midbrain and hypothalamic activation. The overlap of postdromal symptoms and premonitory symptoms leads to further investigation of the nature of postdromal symptoms. Therefore it is thought that migraine is fundamentally due to an abnormality in central processing of not necessarily an abnormal input. Yet in some cases, meningeal nociceptors may also be involved. The exact mechanisms of sensitisation in migraine still remain unknown.

Role of neurochemicals in migraine pathophysiology

The relationship between migraine and alterations in neurochemicals in the central nervous system remains inadequately understood, particularly the possible imbalance between excitatory and inhibitory neurotransmission[63,64]. The activation of the TGVS releases calcitonin gene-related peptide (CGRP) and substance P which further cause vasodilation and neurogenic inflammation through the secretion of inflammatory mediators such as serotonin, adenosine diphosphate, nitric oxide, platelet-activating factor, and interleukins. The vasodilation and neurogenic inflammation further sensitise the neurons in the TG, followed by the neurons in the TNC in the brainstem [63]. It is through this mechanism that CGRP is postulated to transmit nociceptive information.

As regards excitatory-inhibitory neurotransmitter imbalance, there is evidence of a number of anomalies in metabolism of excitatory neurotransmitters in migraine compared with controls. These include altered levels of N-acetyl-aspartylglutamate in the anterior cingulate cortex as well as the insula andhigher glutamate-to-glutamine ratios in the occipital cortex [65,66]. In contrast to evidence for excitatory neurotransmitters, the role of the principal inhibitory neurotransmitter gamma aminobutyric acid (GABA) has only been indirectly demonstrated, for exampleincreased salivary GABA levels have been reported in people with migraine without aura during attacks, compared to interictal periods and to people with non-migraine headaches [67]. Such results suggested that increased GABA metabolism may play a protective mechanism to limit symptomatic episodes. Increased levels of GABA in the cerebrospinal fluid (CSF) are also demonstrated in people with migraine compared to controls [68]. The increased CSF GABA was indicative of increased GABA concentration in the brain due to ischemia.

Despite these findings, the role of GABA in migraine has not been fully established because of the lack of studies directly measuring GABA levels in the brain [69].

Diagnosis and clinical features:

A high index of suspicion is required to diagnose migraine. The migraine aura, consists of visual disturbances with flashing lights or zigzag lines moving across the visual field or of other neurologic symptoms [70], is reported in only 20–25% of patients. Migraine must be differentiated from tension-type headache [71] the most common primary headache syndrome seen in the population. A headache diary can often be helpful in making the diagnosis; it also helps in assessing disability and the frequency of treatment for acute attacks.

Migraine without aura

Description: Recurrent attacks lasting 4–72 hours Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria [48]:

A) At least five attacks fulfilling criteria B–D
B) Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)
C) Headache has at least two of the following four characteristics:
    1. unilateral location
    2. pulsating quality
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D) During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia
E) Not better accounted for by another ICHD-3 diagnosis.

Migraine with aura

Description: Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that develop gradually and are followed by headache and associated migraine symptoms.

Diagnostic criteria [48]:

A) At least two attacks fulfilling criteria B and C

B) One or more of the following fully reversible aura symptoms:
    1. visual
    2. sensory
    3. speech and/or language
    4. motor
    5. brainstem
    6. retinal

C) At least three of the following six characteristics:
    1. at least one aura symptom spreads gradually over >5 minutes
    2. two or more aura symptoms occur in succession
    3. each individual aura symptom lasts 5–60 minutes
    4. at least one aura symptom is unilateral
    5. at least one aura symptom is positive
    6. the aura is accompanied, or followed within 60 minutes, by headache

E) Not better accounted for by another ICHD-3 diagnosis.

Chronic migraine

Description: Headache occurring on 15 or more days/ month for more than three months, which, on at least eight days/month, and has the features of migraine headache.

Diagnostic criteria [48]:

A) Headache (migraine-like or tension-type-like) on >15 days/month for >3 months, and fulfilling criteria B and C

B) Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 Migraine with- out aura and/or criteria B and C for 1.2 Migraine with aura

C) On >8 days/month for >3 months, fulfilling any of the following:
    1. criteria C and D for 1.1 Migraine without aura
    2. criteria B and C for 1.2 Migraine with aura
    3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D) Not better accounted for by another ICHD-3 diagnosis.

Management

After establishing the diagnosis of migraine, it is important to assess the extent of a patient's disease and disability. We followed up our patients with a headache diary, which included headache days, severity of pain (visual analog scale), duration of pain and preventive medication.

Acute attack therapies for migraine:

The mainstay of pharmacologic therapy is, judicious use of one or more of the many medicines that are effective in migraine. The selection of the optimal regimen [72]depends on a number of factors, the most important of which is the severity of the attack.

Mild migraine attacks can be managed by oral agents; the average efficacy rate is 50– 70%. Severe migraine attacks usually require parenteral therapy. Most drugs effective in the treatment of migraine are members of one of three major pharmacologic classes: nonsteroidal anti-inflammatory drugs, 5-HT1B/1D receptor agonists, and dopamine receptor antagonists.

An adequate dose of whichever agent is chosen should be used as soon as possible after the onset of an attack. If additional medication is required within 60 min because symptoms return or have not subsided, the first dose should be increased for subsequent attacks or a different class of drug tried as first-line treatment.

Migraine therapy must be individualized; a standard approach for all patients is not possible. A therapeutic regimen may need to be constantly refined until one identifies an optimal regimen which provides the patient with rapid, complete and consistent relief with minimal side effects.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):

The severity and duration of a migraine attack can be reduced significantly by NSAIDs. Many undiagnosed migraineurs self-treat with non-prescription NSAIDs. A general consensus is that NSAIDs are most effective when taken early in the attack. However, the effectiveness of these agents is usually less than optimal in moderate or severe migraine attacks. The combination of acetaminophen, aspirin, and caffeine is approved for use by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate migraine. The combination of aspirin and metoclopramide has shown to be comparable to a single dose of oral sumatriptan. Important side effects of NSAIDs include dyspepsia and gastrointestinal irritation.

5-HT1B/1D Receptor agonists:

Oral Stimulation of 5-HT1B/1D receptors can control an acute migraine attack. Ergotamine and dihydroergotamine are nonselective receptor agonists, whereas the triptans are selective 5-HT1B/1D receptor agonists. Each drug in the triptan class has similar pharmacologic properties but varies slightly in terms of clinical efficacy. A variety of triptans, 5-HT1B/1D receptor agonists— sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, and zolmitriptan—are now available for the treatment of migraine. Rizatriptan andeletriptan are the most efficacious of the triptans. Sumatriptan and zolmitriptan have similar rates of efficacy as well as time to onset, with an advantage of having multiple formulations, almotriptan has a similar rate of efficacy to sumatriptan and is better tolerated, and frovatriptan and naratriptanare somewhat slower in onset but are better tolerated. Clinical efficacy appears to be related more to the tmax (time to peak

plasma level) than to the potency, half-life, or bioavailability. This observation is consistent with a large set of data indicating that faster acting analgesics are more effective than slower-acting agents.

Monotherapy with a selective oral 5-HT1B/1D receptor agonist does not result in rapid, and complete relief of migraine in all patients. Triptans are generally not effective in migraine with aura unless it is given after the aura is completed and the headache initiated. Side effects are common, although often mild and transient. 5-HT1B/1D receptor agonists are contraindicated in individuals with a history of cardiovascular and cerebrovascular disease.

Recurrence of headache, within usual time course of an attack, is another limitation of triptan use and occurs at least occasionally in most patients. Evidence from randomized controlled trials has shown that co-administration of a longer-acting NSAID, naproxen 500 mg, with sumatriptan will augment the initial effect of sumatriptan and, reduce rates of headache recurrence. Ergotamine preparations offer a nonselective means of stimulating5-HT1 receptors. A non-nauseating dose of ergotamine should be sought because a dose that precipitates nausea is too high and may intensify head pain. Except for a sublingual formulation of ergotamine, oral formulations of ergotamine also contain 100 mg caffeine. The average oral ergotamine dose for a migraine attack is 2 mg. The clinical studies demonstrating efficacy of ergotamine in migraine predated the clinical trial methodologies used with the triptans, it is difficult to assess the clinical efficacy of ergotamine versus the triptans. Ergotamine appears to have a much higher incidence of nausea than triptans but less headache recurrence.

Nasal formulations of dihydroergotamine[73](Migranal), zolmitriptan (Zomig nasal) or sumatriptan are useful in patients requiring a non-oral route of administration. The nasal sprays result in substantial blood levels within 30–60 min. Although in theory nasal sprays might provide faster and more effective relief of a migraine attack than oral formulations, their reported efficacy is only approximately 50– 60%.

Studies with a new inhalational formulation of dihydroergotamine are indicative that its absorption problems can be overcome to produce rapid onset of action with good tolerability.

Parenteral Administration of drugs by injection, such as dihydroergotamine and sumatriptan, is approved by the FDA for the rapid relief of a migraine attack. Peak plasma levels of dihydroergotamine is achieved 3 min after IV dosing, 30 min after IM dosing, and 45 min after SC dosing. If an attack has not already peaked, SC or IM administration of 1 mg of dihydroergotamine suffices for more than80–90% of patients. Sumatriptan, 4–6 mg SC, is effective in ~50–80% of patients and can now be administered by a needle-free device.

Dopamine receptor antagonists:

Oral dopamine receptor antagonists are considered as adjunctive therapy in migraine. Drug absorption is impaired during migraine because of reduced gastrointestinal motility. Delayed absorption occurs in the absence of nausea and is related to the severity of the attack and not its duration. Therefore, whenever oral NSAIDs and/or triptan agents fail, the addition of a dopamine receptor antagonist, such as metoclopramide 10 mg or domperidone 10 mg, should be considered to enhance gastric absorption. Dopamine receptor antagonists decrease nausea/vomiting and restore normal gastric motility.

Parenteral Dopamine receptor antagonists (e.g., chlorpromazine, prochlorperazine, metoclopramide) by injection can also provide significant acute relief of migraine; they can be used in combination with parenteral 5-HT1B/1D receptor agonists. A common IV protocol used for the treatment of severe migraine is the administration over 2 min of a mixture of 5 mg of prochlorperazine and 0.5 mg of dihydroergotamine.

Other medications for acute migraine attack:

Nasal preparation of butorphanol is available for the treatment of acute pain. As with all opioids, the use of nasal butorphanol has little role in migraine treatment.

Oral: The combination of acetaminophen, dichloralphenazone, and isometheptene, one to two capsules, has been classified by the FDA as —effective in the treatment of migraine. The clinical studies demonstrating the efficacy of this combination analgesic in migraine predated the clinical trial methodologies used with the triptans, it is difficult to compare the efficacy of this sympathomimetic compound to other agents.

Parenteral Opioids are modestly effective in the acute treatment of migraine. For example, IV meperidine (50–100 mg) is given frequently in the emergency room. This regimen —works in the sense that the pain of migraine is eliminated. However, this regimen is clearly suboptimal for patients with recurrent headache.. Patients taking oral opioids, such asoxycodone or hydrocodone, habituation or addiction can greatly confuse the treatment of migraine. Opioids do not treat the underlying headache mechanism; rather, they act to alter the pain sensation, and there is evidence their use may decrease the likelihood of a response to triptans in the future. Opioid craving and/or withdrawal can aggravate and accentuate migraine. It is recommended that opioid use in migraine be limited to patients with severe, but infrequent, headaches that are unresponsive to other pharmacologic approaches or who have contraindications to other therapies.

Preventive treatment for migraine:

Patients with an increasing frequency of migraine attacks or with attacks that are either unresponsive or poorly responsive to abortive treatments are good candidates for preventive agents.[74]

A preventive medication should be considered in the subset of patients with four or more attacks a month. The mechanism of action of these

drugs is unclear; it seems likely that the brain sensitivity that underlies migraine is modified. Significant side effects are associated with the use of many of these agents; determination of dose can be difficult because the recommended doses have been derived for conditions other than migraine. Patients are usually started on a low dose of a chosen treatment; the dose is then gradually increased, up to a reasonable maximum, to achieve clinical benefit. Drugs must be taken daily, and there is usually a lag of between 2 to 12 weeks before an effect is seen.

The drugs that have been approved by the FDA for the prophylactic treatment of migraine include propranolol, timolol, sodium valproate, topiramate, and methysergide.

A number of other drugs appear to display prophylactic efficacy. This group includes amitriptyline, nortriptyline, flunarizine, phenelzine, gabapentin, and cyproheptadine.

The mechanism of action of these drugs is unclear; it seems likely that the brain sensitivity that underlies migraine is modified. Phenelzine and methysergide are usually reserved for resistant cases because of their serious potential side effects. If these agents fail or lead to unacceptable side effects, second-line agents such as methysergide or phenelzine can be used. Once effective stabilization is achieved, the drug is continued for ~6 months and then slowly tapered to assess the continued need. Many patients are able to discontinue medication and experience fewer and milder attacks for long periods, suggesting that these drugs may alter the natural history of migraine.

The presence of calcitonin gene-related peptide (CGRP) in the trigeminovascular system, the induction of a migraine-like headache after intravenous administration of exogenous CGRP and the observation of CGRP release during the headache phase of a migraine attack, have led to the assumption that it plays a major role in the pathophysiology of migraine. The discovery of this new drug target

resulted in the development of the first disease-specific preventive treatment class for chronic migraine, being monoclonal antibodies against the CGRP molecule (eptinezumab, fremanezumab and galcanezumab) or its receptor complex (erenumab) (CGRP mAb).

Onabotulinum toxin type A in migraine:

Placebo-controlled trials of onabotulinum toxin type A in episodic migraine were negative, whereas, overall, placebo- controlled trials in chronic migraine were positive.

A double-blind, randomized, 90-day placebo-controlled study to determine the safety and efficacy of botulinum toxin type A in prophylaxis of 30 adult migraine patients. which concluded that botulinum toxin type A injections were well tolerated and provided effective migraine prophylaxis in these patients, the injection produced significantly greater reductions in the frequency of migraine attacks of any severity at Day 90 (-3.14 vs. - 0.53; $p<0.05$) and in the frequency of severe migraine attacks at Days 60 (-1.4 vs. -0.54; $p<0.05$) and 90 (-.8 vs. -0.20; $p<0.02$)[75].

Another Double-Blind, Randomized, Placebo-Controlled trial To assess the efficacy, safety, and tolerability of onabotulinumtoxinA as headache prophylaxis in adults with chronic migraine was conducted. Pooled analyses demonstrated a large mean decrease from baseline in frequency of headache days, with statistically significant between-group differences favouring onabotulinumtoxinA over placebo at week 24 and at all other time points. Significant differences favouring onabotulinumtoxinA were also observed for all secondary efficacy variables at all time points, with the exception of frequency of acute headache pain medication intakes.[76]

In 2019 an open-label, prospective study to assess the efficacy and safety of onabotulinumtoxin A in people with chronic migraine was performed, it assessed 641 patients with complete daily diary records at baseline. The results of their study indicated that

onabotulinumtoxinA was associated with reductions from baseline in headache-day frequency and improvements in disability and quality of life for up to 108 weeks in people with CM with daily headache; however, a longer duration of treatment was required to fully realize the treatment effect on headache. No new safety concerns were identified.[77]

REPOSE was a 2-year prospective, multicentre, non-interventional, observational study to describe the real-world use of onabotulinumtoxinA in adult patients with CM. It demonstrated that onabotulinumtoxinA treatment is associated with decreased health resource utilization and supports the long-term benefits associated with the use of onabotulinumtoxinA for chronic migraine in clinical practice.[78]

The PREEMPT protocol for onabotulinum toxin A injections is the only FDA-approved injection pattern for chronic migraine, and practitioners are specially trained in its administration. In our study we followed PREEMPT protocol for administration of onabotulinum toxin-A injection.

Greater occipital nerve block in migraine:

The greater occipital nerve (GON) originates in the dorsal ramus of the C_2 as well as the C_3 segments of the spinal cord and comprises sensory fibers alone. Its sensory distribution path- way includes the posterior part of the head and extends anteriorly toward the vertex, becoming superficial at the infero lateral aspect of the occipital protuberance. It is thought that sensory input from the GON and the ophthalmic branch of the trigeminal nerve converges into the trigeminal nucleus caudalis, which is hypothesized to be the reason why occipital neuralgia is sometimes associated with migraine headache symptomatology. GON block decreases afferent input to the trigeminal nucleus caudalis, resulting in central pain modulation and reducing neuronal hyper excitability at the level of second-order neurons.

The procedure to inject the GON involves inserting a needle into the infero lateral aspect of the occipital protuberance and injecting a combination of local anaesthetic and a corticosteroid. We used a mixture of 3 mL of 2% lidocaine and 80mg of methylprednisolone in our study.

A prominent improvement in quality of life and disability rates of chronic migraine patients treated with GONB compared to pre-treatment has been seen in earlier studies[79].

A randomized controlled trial to determine the effectiveness of greater occipital never block on headache in patients with chronic migraine was conducted in 2017 and it was found that the number of attacks were significantly decreased during 6 weeks follow up ($p<0.05$). Mean headache severity was significantly decreased during first and second two-week follow up by 3.04 and 2.39 points, respectively[80].

GON blockade with bupivacaine was superior to placebo and was found to be effective, safe, and cost-effective for the treatment of CM. The decrease in the monthly average pain intensity score on the injected side was statistically significant in the treatment group of many randomized controlled trials.[81-83]

Materials and Methods

This prospective, observational and non-blinded study was conducted to know the efficacy, safety and adverse effects of Botulinum toxin and greater occipital nerve block in patients with chronic migraine.

SOURCE OF DATA

Data collection was done from all follow up and new patients presenting with chronic migraine (defined according to the 2018 International Classification of headache disorder ICHD-3) participating in Botulinum toxin or greater occipital nerve block to Neurology OPD Dayanand medical college and hospital ludhiana from March 2020 to October 2021 after taking informed and written consent.

METHOD OF COLLECTION OF DATA

Inclusion Criteria

Patient who presented to DMCH/HDHI in patient/ out-patient neurology clinic:

Age ≥ 18 years and ≤ 80years

Adult with chronic migraine (defined according to the 2018 International Classification of headache disorder ICHD-3)

Exclusion criteria

1. Age < 18 years
2. Patients who have intracranial space occupying lesion
3. Patients with a concomitant medical illness such as end-stage organ failures e.g., renal, cardiac, hepatic, respiratory, secondary causes of chronic daily headache.
4. Pregnant females

METHOD OF INTERVENTION

All patients attending the Neurology OPD Dayanand medical college and hospital Ludhiana from March 2020 to October 2021 who gave informed and written consent for a GONB injection or Botulinum toxin injection were assessed. The injection was offered to patients with chronic migraine, due to the on-going pandemic of COVID-19 the

number of subjects enrolled in the study were less as the overall out-patient number was less.

After enrolling the patient once the desired criteria was met, a detailed history with headache days 4 weeks prior to intervention, severity of headache according to visual analogue scale on most of the days, trigger factors precipitating the migraine, prophylactic medication and analgesic use were documented. All patients had a normal neuroimaging in the form of NCCT head/ MRI Brain.

Patients were explained in detail about the procedure and they were free to choose between greater occipital nerve block and onabotulinum toxin type-A injection.

All patients were observed for at-least one hour post intervention.

TECHNIQUE FOR GONB

The ultrasound-guided GONB more accurately locate the nerve. The patient is face down on the table. To locate the nerve, we look for the occipital artery in the medial one-third of the superior nuchal line between the occipital tubercle and mastoid process. GONB was performed by applying the injection to the medial of the artery.

A 22-gauge needle is advanced beneath the lateral border of the probe using real-time ultrasound guidance and an in-plane technique. The occipital nerve is seen medial to the artery. Mixture of 3 mL of 2% lidocaine and 80mg of methylprednisolone is given for GON block.

The continuous diary filling was mandatory to assess response to treatment in order to determine whether patients were offered a repeat treatment.

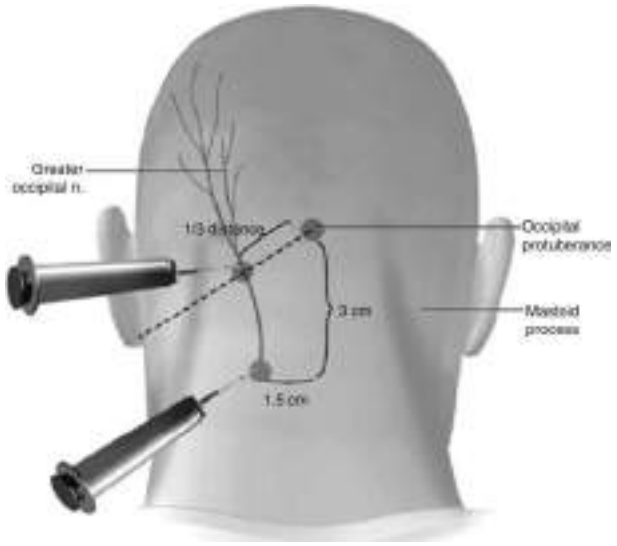


Figure 2. Sites of distal and proximal GONB

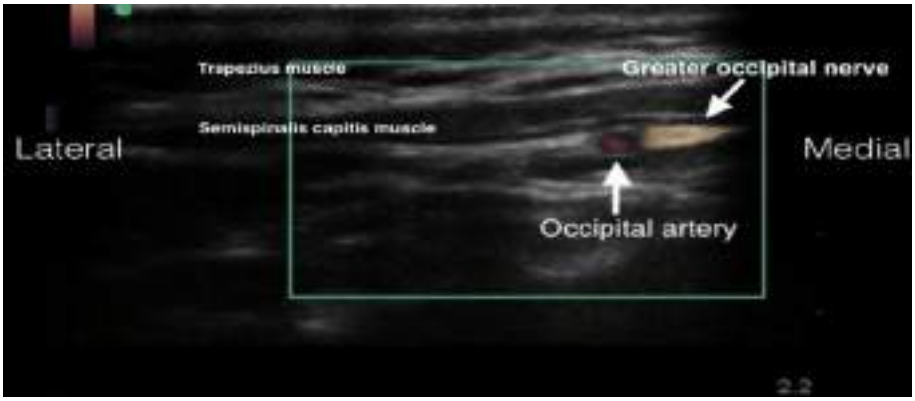


Figure 3.Ultrasound-Guided greater Occipital Nerve localisation

TECHNIQUE FOR ONA-BOTULINUM TOXIN TYPE A

The 2 clinical trials that led to FDA approval used a standardized set of injections called the PHASE III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol. With this protocol, developed and tested extensively, 31 small injections of 5 units each are placed at prescribed locations over the forehead, sides of the head, and back of the head and neck.

The PREEMPT protocol for onabot injections is the only FDA-approved injection pattern for chronic migraine, and practitioners are specially trained in its administration [84].

With this protocol, developed and tested extensively, 31 small injections of 5 units each are placed at prescribed locations over the forehead, sides of the head, and back of the head and neck. The injections are just under the skin, creating a small bubble or wheal at the site that is usually not visible beyond a few hours

The amount of medicine approved by the FDA for chronic migraine prevention, and administered in the PREEMPT protocol, is 155 units. The paradigm includes follow the pain injections of up to further 45 units, although none of our patients received additional injections.

The continuous diary filling was mandatory to assess response to treatment in order to determine whether patients were offered a repeat treatment.

MUSCLE AREA	RECOMMENDED DOSE/NUMBER OF SITES
Corrugator	10 Units divided between 2 sites
Procerus	5 Units in 1 site
Frontalis	20 Units divided between 4 sites
Temporalis	40 Units divided between 8 sites
Occipitalis	30 Units divided between 6 sites
Cervical paraspinal	20 Units divided between 4 sites
Trapezius	30 Units divided between 6 sites
TOTAL DOSE	155 Units† divided between 31 sites

Figure 4. Recommended dose and site of onabotulinum toxin-A according to PREEMPT protocol[84]

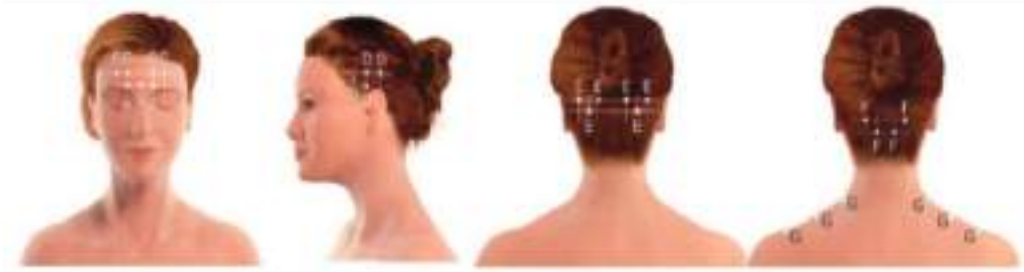
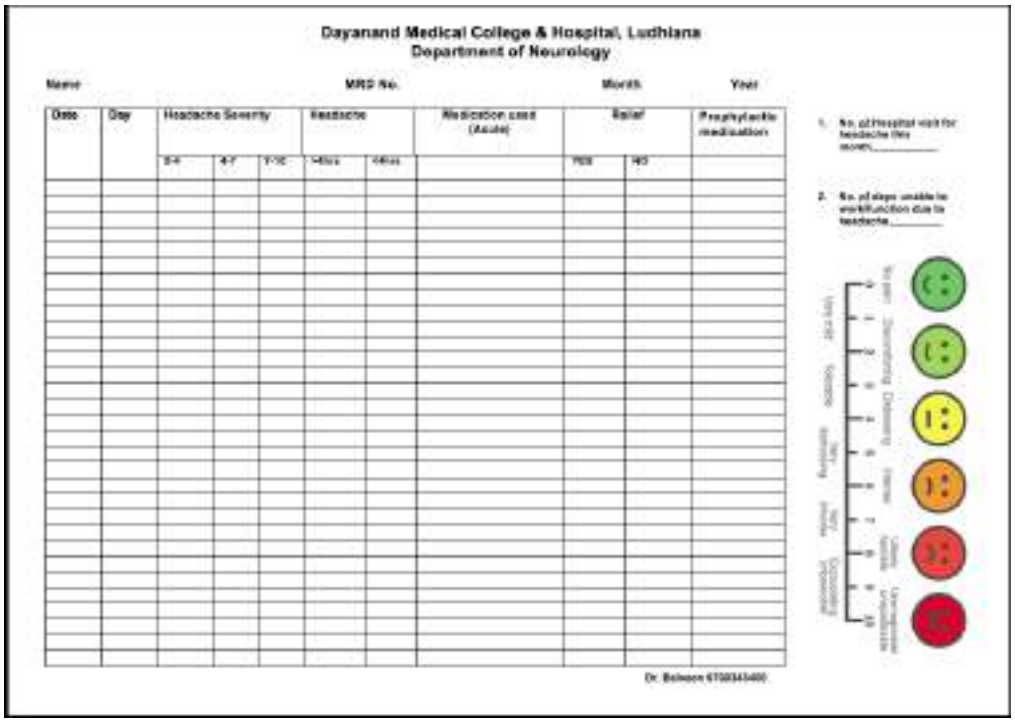


Figure 5. Recommended site of onabotulinum toxin-A according to PREEMPT protocol [84]

Follow up criteria

Patients were asked to fill in a headache diary for four weeks following the injection; headache diary includes headache days, severity of headache according to VAS (visual analogue scale), duration of headache, and medication used at the time of attack. Patient were followed up after every week, for four weeks.


Dayanand Medical College & Hospital, Ludhiana
Department of Neurology

Name MRD No. Month Year

Date	Day	Headache Severity			Headache		Medication used (Acute)	Relief		Prophylactic medication

1. No. of Hospital visit for headache this month_____

2. No. of days unable to work/function due to headache_____

Figure 6. Headache diary

Efficacy Measures.—The primary efficacy measure was the mean change from baseline in the frequency of headache-free days in a 4 week period for the GONB and BOTOX group, determined from data recorded by patients in the headache diary.

The primary visit for determination of efficacy was weekly, with the evaluation reflecting the prior 30-day period. Baseline for the efficacy measures was defined as the frequency of headache-free days during the first 28 days of the study. A headache-free day was defined as a complete day (clock time of 00:00 to 23:59) in which no headache was recorded.

A secondary efficacy measure was comparison of severity of headache according to visual analogue scale pain Score before and after intervention. Headache severity was recorded using a VAS Visual Analog Scale (VAS), all patients were informed about the scale numbered from 0 (no pain) to 10 (worst pain) and were asked to indicate pain severity with VAS in the headache diary. Headache severity was categorised into mild (VAS 0-4), moderate (VAS 4-7) and severe (VAS 7-10).

Safety Measures.—Safety was assessed by reports of adverse events, physical and neurological examinations, and clinical laboratory tests. At each visit following treatment at day 0, adverse events were recorded and documented with information regarding the date of onset, resolution date (if applicable), severity (mild, moderate, or severe), duration, frequency, relationship to study treatment, action taken regarding study treatment, treatment required (if any), and outcome.

PRIOR AND CONCOMITANT THERAPY

The use of any concurrent medication (e.g., prescription [including prophylactic medications] or over-the-counter [including herbal remedies]) was recorded along with the reason that a medication was taken and the medications were continued as prescribed.

OUTCOME

The efficacy, safety and adverse effects of Botulinum toxin and greater occipital nerve block in patients with chronic migraine would be known by this study.

Primary endpoint of the study was monthly headache days before and after the intervention

Secondary endpoints were comparison of severity of headache according to visual analogue scale pain Score before and after intervention and safety outcome of intervention.

Headache diary was given to the patient and the headache days and severity according to visual analogue scale was assessed on follow up after 4 weeks.

STATISTICAL ANALYSIS

Data were described in terms of range; mean ±standard deviation (± SD), median (IQR), frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups was done using Repeated ANOVA .A probability value (*p* value)less than 0.05 was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

Observations & Results

A total of 20 eligible patients consented to participate. Data collection was done from all follow up and new patients coming to outpatient department at DMCH Ludhiana from March 2020 to October 2021, who presented with chronic migraine (defined according to the 2018 International Classification of headache disorder ICHD-3) and participated in Botulinum toxin injection or greater occipital nerve block after informed and written consent.

Four patients participated in botulinum toxin injection group and sixteen patients participated in greater occipital nerve block.

Baseline demographics in botox group

Among the patients who received Botox Injection, all were females, and the mean age was 42.25 years (range 33-55 years). The patients complained of a mean headache duration of 13.00 years (range 7-20 years). Out of the 4 patients, 2 reported a mean headache severity of 0-4 (visual analog scale) while 2 patients had a mean headache severity of 4-7 (visual analog scale) prior to injection.

The baseline frequency of days with migrainous headache ranged from 20 to 28 days per 28-day period, with a mean of 26.00 days (SD 4.0).

When we compared the headache locations in the 4 patients, 2 had a left hemicranial headache, 1 had a right hemicranial headache while 1 had holocranial headache.

Table 3: Baseline demographics in botox group

	Botox group
N	4
Age (y), mean (SD)	42.25
Female	4
Headache duration (years), mean (SD)	13.00
Headache location	
Left hemicranial	2
Right hemicranial	1
Holocranial	1
Occipital	0
Triggers	
None	0
Fasting	0
Sleep deprivation	0
Weather change	0
Travelling	0
Sleep deprivation, fasting	1
Stress, sleep deprivation, weather change	0
Travelling, fasting	0
Travelling, sleep deprivation	1
Travelling, sleep deprivation, fasting, stress	1
Travelling, sleep deprivation, stress	1
Travelling, sleep deprivation, weather change	0
Headache days (last 4 weeks)	26.00

Baseline demographics in GONB group

Among the patients who received GONB, the mean age was 42.13 years (range 24-74 years) and 13 patients were female (81.3%). The patients had a mean headache duration of 13.44 years (range 1-40 years). Out of the 16 patients, 2 had mean headache severity of 0-4 (visual analog scale), 6 patients had mean headache severity of 4-7 (visual analog scale) and 8 patients had mean headache severity of 7-10 (visual analog scale).

Patients had a mean of 22.63 (range 15-28) headache days prior to injection in last 4 weeks.

The baseline frequency of days with migrainous headache ranged from 15 to 28 days per 28-day period, with a mean of 22.63 days (SD 5.1).

On comparing the headache locations in the patients who received GONB, 4 patients had left and right hemicranial headache each, 7 had holocranial while 1 had occipital headache.

Table 4. Baseline demographics in GONB group

	GONB group
N	16
Age (y), mean (SD)	42.13
Female	13
Headache duration (years), mean (SD)	13.44
Headache location	
Left hemicranial	4
Right hemicranial	4
Holocranial	7
Occipital	1
Triggers	
None	2
Fasting	1
Sleep deprivation	1
Weather change	1
Travelling	1
Sleep deprivation, fasting	2
Stress, sleep deprivation, weather change	1
Travelling, fasting	1
Travelling, sleep deprivation	3
Travelling, sleep deprivation, fasting, stress	1
Travelling, sleep deprivation, stress	1
Travelling, sleep deprivation, weather change	1
Headache days (last 4 weeks)	22.63

Trigger factors

On assessing the trigger factors, sleep deprivation, fasting, travelling, stress were the common trigger factors in the two groups.

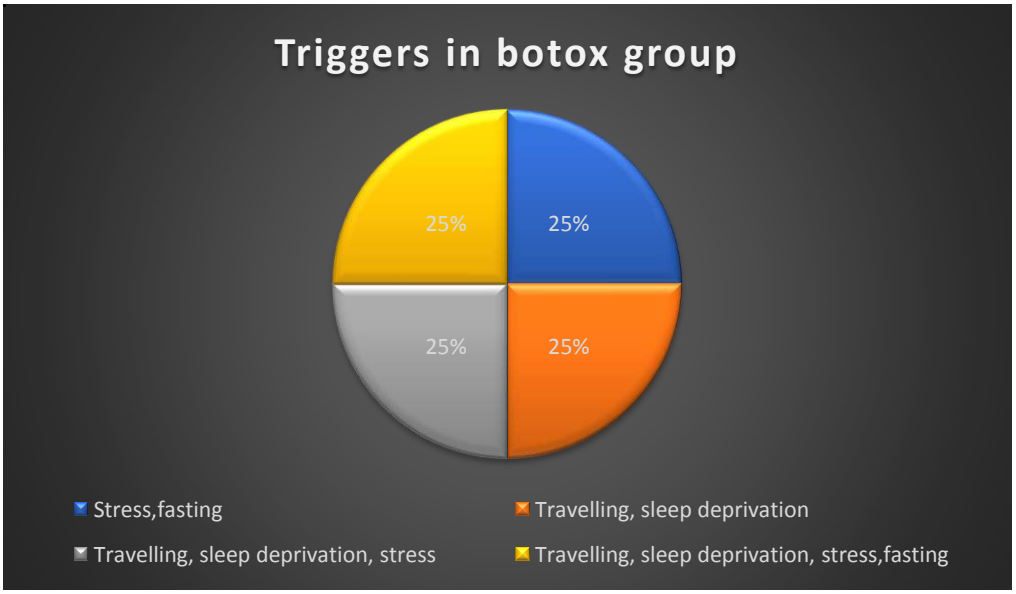


Figure 7: Triggers for migraine in botox group

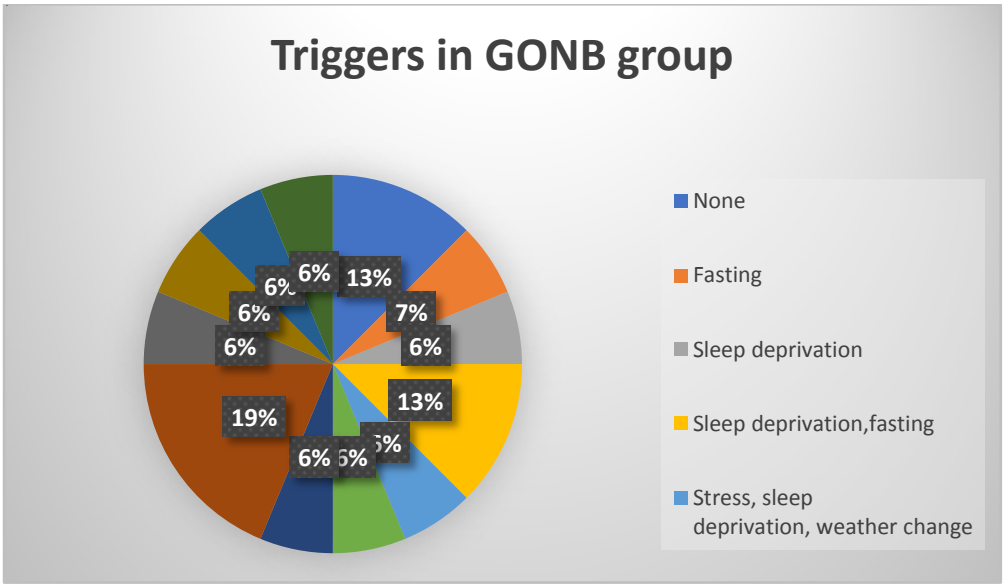


Figure 8: Triggers for migraine involved in GONB group

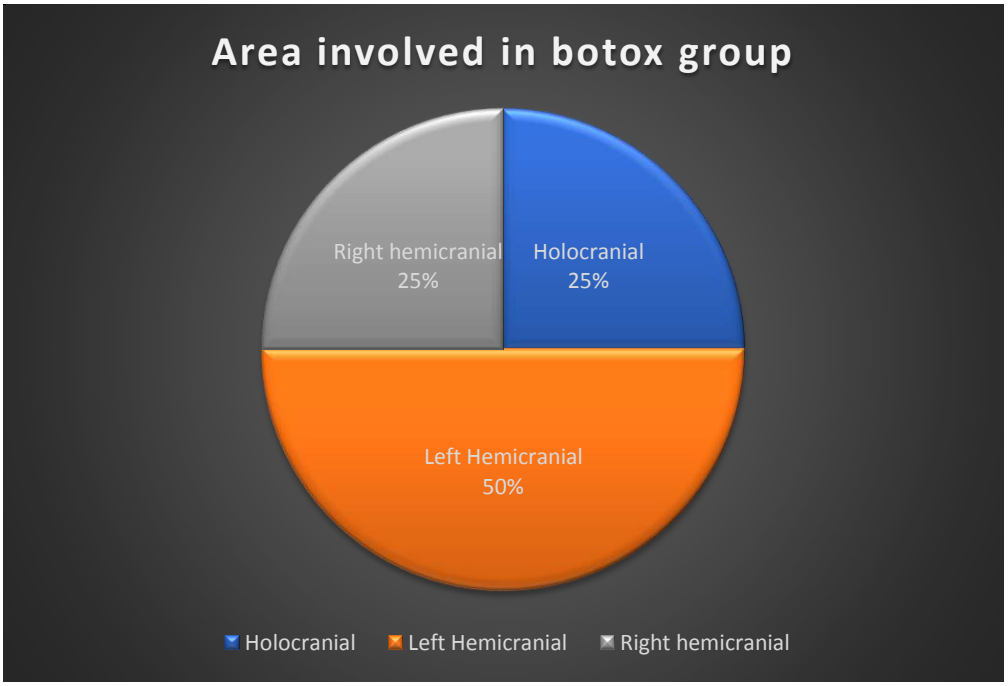


Figure 9: Area involved in botox group

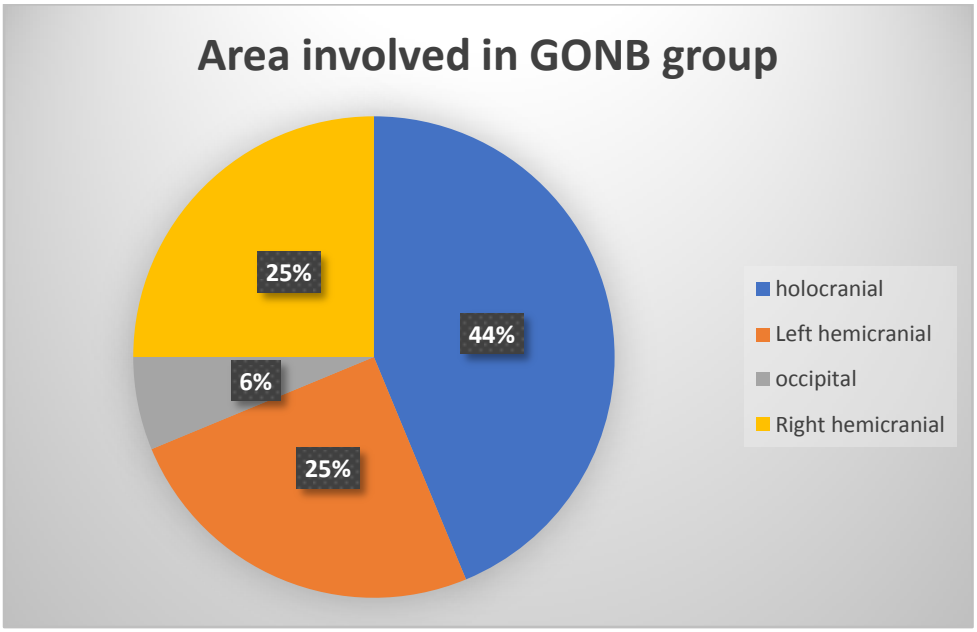


Figure 10. Area involved in botox group

Outcome data

Primary Endpoint: Monthly Headache Days

In the last 4 weeks prior to the Botox injection, on an average, the patients complained of 26 days of headache while after the injection, the mean duration reduced to 12 headache days.

On comparing the headache free days post injection, in the first week, the patients had 2 mean headache free days which increased successively to 3 in the second, 4 in the third and 5.75 mean headache free days in the fourth week post injection. Four weeks post the injection, patients reported a mean of 15.75 headache free days.

On comparing the GONB group, the patients had an average number of 22.63 headache days prior to the injection in the last 4 weeks, while after the injection, it reduced to 10.81 mean headache days. In the first week post GONB, the mean number of headache free days were 5.81, which reduced to 4.69 in the second and 4.00 in the third week, while in the fourth week post injection, the mean headache free days reduced to 2.69. Four weeks post the injection, the mean headache free days reduced to 17.19.

Table 5 Comparison of Headache days prior and after the BOTOX injection

	N	Mean	SD	Minimum	Maximum	Median	IQR
Headache days prior to injection in last 4 weeks	4	26.00	4.000	20	28	28.00	22-28
Headache days after injection	4	12.25	5.123	5	17	13.50	7-16.25

Table 6: Headache free days after the BOTOX injection

Headache free days	N	Mean	SD	Minimum	Maximum	Median	IQR
week 1	4	2.25	1.258	1	4	2.00	1.25-3.5
week 2	4	3.25	2.062	1	6	3.00	1.5-5.25
week 3	4	4.50	.577	4	5	4.50	4-5
week 4	4	5.75	1.500	5	8	5.00	5-7.25

	N	Mean	SD	Minimum	Maximum	Median	IQR
Headache free days after 4 weeks	4	15.75	5.123	11	23	14.50	11.75-21

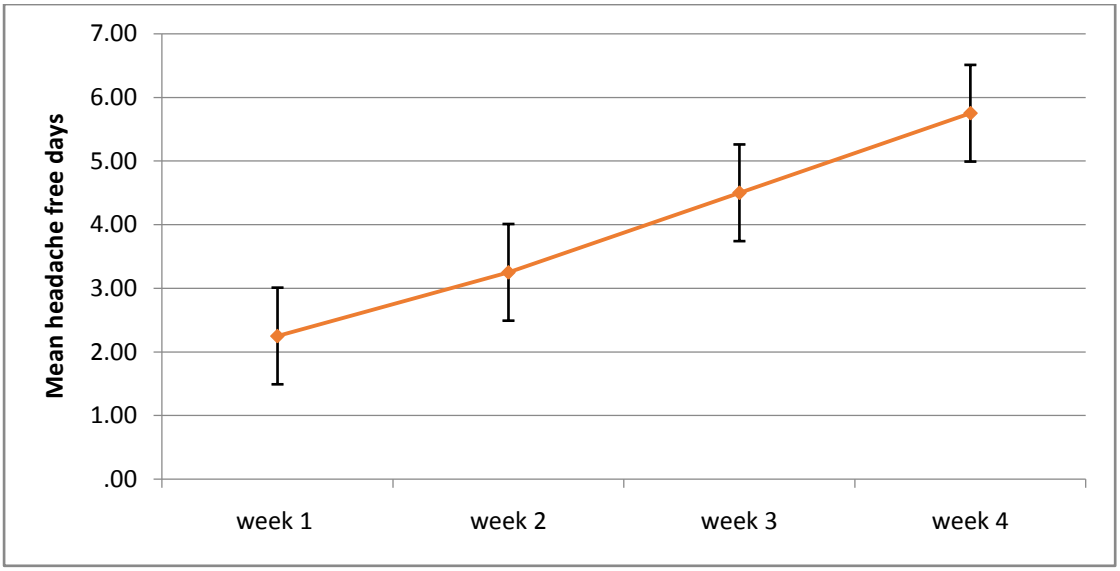


Figure 11: Headache free days after the BOTOX injection

Table 7 Comparison of Headache days prior and after the GONB injection

	N	Mean	SD	Minimum	Maximum	Median	IQR
Headache days prior to injection in last 4 weeks	16	22.63	5.188	15	28	20.00	20-28
Headache days after injection	16	10.81	6.327	2	23	10.00	6.25-14.75

Table 8 Headache free days after the GONB injection

	N	Mean	SD	Minimum	Maximum	Median	IQR
Headache free days in week 1	16	5.81	1.424	2	7	6.00	5.25-7
Headache free days in week 2	16	4.69	1.887	1	7	5.00	3.25-6
Headache free days in week 3	16	4.00	1.932	1	7	4.00	3-5
Headache free days in week 4	16	2.69	1.662	0	5	2.50	1-4

	N	Mean	SD	Minimum	Maximum	Median	IQR
Headache free days after 4 weeks	16	17.19	6.327	5	26	18.00	13.25-21.75

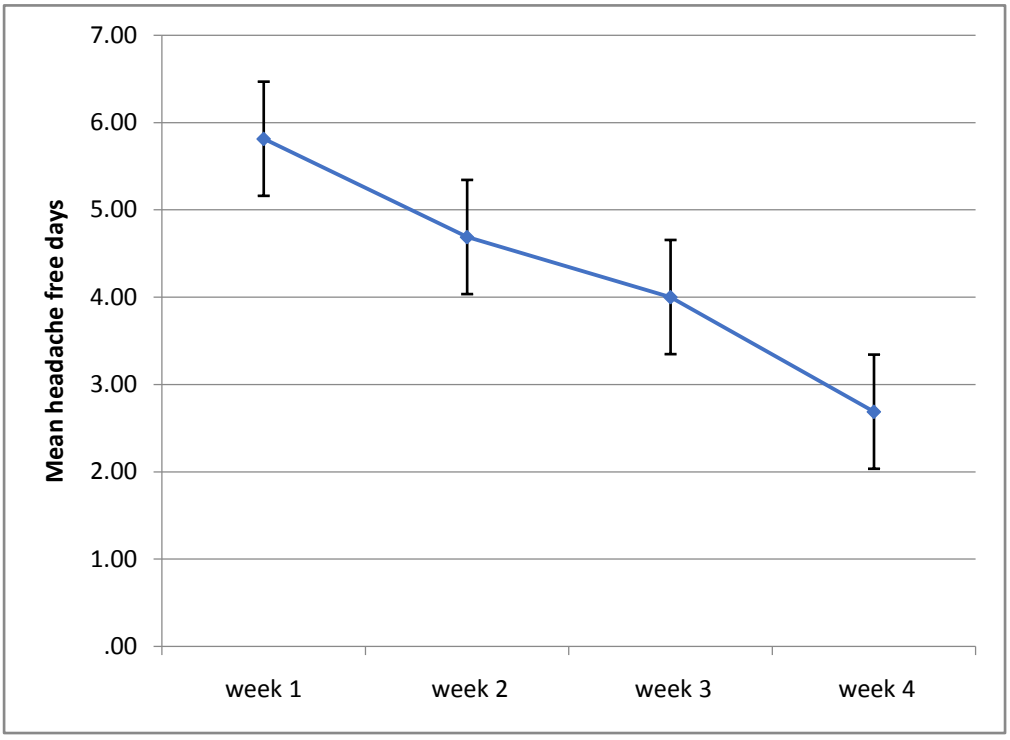


Figure 12: Headache free days after the GONB injection

Visual Analogue Scale Pain Score before and after intervention

Prior to the Botox injection, among the 4 patients, the mean headache severity in terms of Visual Analog Scale was in the range 4-7 for 2 patients, while it was severe 7-10 for 2 patients.

Table 9 Mean headache severity prior to BOTOX injection (visual analog scale)

Mean headache severity prior to injection (visual analog scale)	No. of cases	Percentage
4-7	2	50.0
7-10	2	50.0
Total	4	100.0

After the Botox Injection, we compared the number of headache days on the basis of severity. It was observed that the number of headache days with higher severity reduced. The patients had 7 mean headache days with severity 0-4, while they had 3.75 mean headache days with severity 4-7 and only 1.5 mean headache days with severity 7-10 on the Visual Analog Scale.

Table 10: Mean headache severity after BOTOX injection (visual analog scale)

	N	Mean	SD	Minimum	Maximum	Median	IQR
Headache days with severity 0-4 (visual analog scale) after injection	4	7.00	2.449	5	10	6.50	5-9.5
Headache days with severity 4-7 (visual analog scale) after injection	4	3.75	3.304	0	7	4.00	0.5-6.75
Headache days with severity 7-10 (visual analog scale) after injection	4	1.50	1.000	0	2	2.00	0.5-2

Prior to the GONB injection, among the 16 patients who received it, 8 had a mean headache severity in the range 7-10, while 6 patients had a severity range of 4-7 and 2 had a severity range of 0-4.

Table 11 Mean headache severity prior to GONB injection (visual analog scale)

Mean headache severity prior to injection (visual analog scale)	No. of cases	Percentage
0-4	2	12.5%
4-7	6	37.5%
7-10	8	50.0%
Total	16	100.0%

After the GONB Injection, the number of headache days were compared on the basis of severity. We observed that the number of headache days with higher severity reduced in this group as well. While the patients had 7.31 mean headache days with severity 0-4, they had 2.63 mean headache days with severity 4-7 and only 0.88 mean headache days with severity 7-10 on the Visual Analog Scale.

Table 12 Mean headache severity after GONB injection (visual analog scale)

	N	Mean	SD	Minimum	Maximum	Median	IQR
Headache days with severity 0-4 (visual analog scale) after injection	16	7.31	6.671	0	20	5.00	3.25-9.25
Headache days with severity 4-7 (visual analog scale) after injection	16	2.63	2.187	0	7	2.00	0.5-4.5
Headache days with severity 7-10 (visual analog scale) after injection	16	.88	1.258	0	4	.00	0-2

Safety outcome of intervention

Adverse events during follow-up were assessed for all 20 patients in the Botox and GONB group. No serious adverse events were reported in the both the groups, however a relatively few adverse effects were reported. Injection site pain lasting <24 hours was noted in one patient and one patient observed fatigue for 5 days post intervention in the botox group.

Injection site pain lasting <1 hour was noted in four patients following the injection in the GONB group. There was no statistically significant difference in adverse events between the Botox and GONB groups.

Table 13: Adverse events in BOTOX group.

	Botox group
N	04
Injection site pain	1
Abdominal distension	0
Injection site paresthesia	0
Fatigue	1
Nausea	0
Pain (unspecified)	0
Vasovagal syncopal	0

Table 14: Adverse events in GONB group.

	GONB group
N	16
Injection site pain	4
Abdominal distension	0
Injection site paresthesia	0
Fatigue	0
Nausea	2
Pain (unspecified)	1
Vasovagal syncopal	0

Table 15: Adverse events in BOTOX and GONB groups.

	Botox group	GONB group
N	04	16
Any adverse event	2	7
Any serious adverse event	0	0

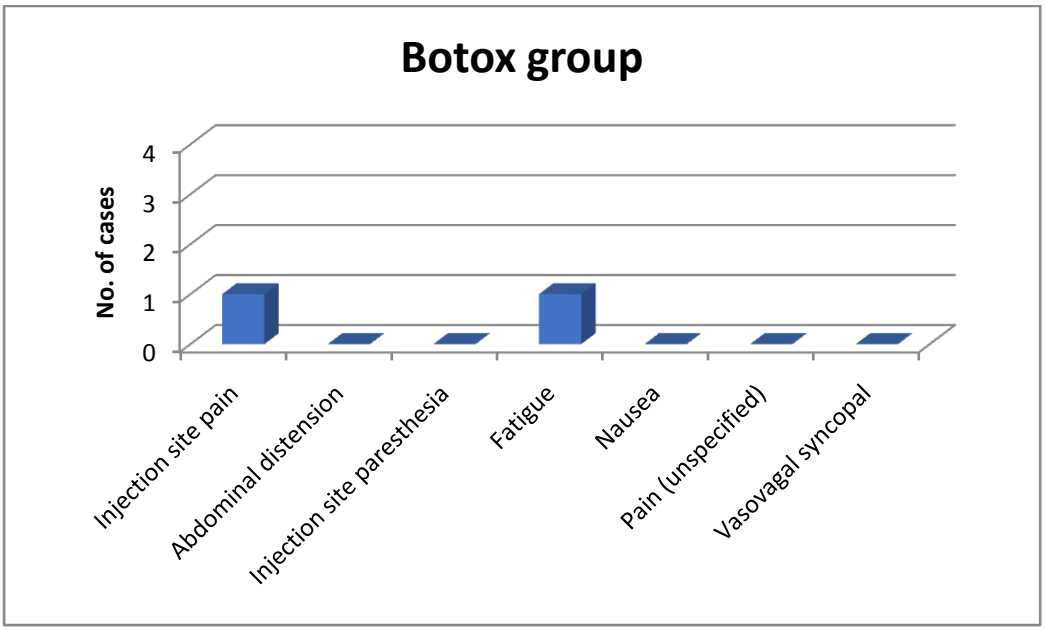


Figure 13: Adverse events in BOTOX group.

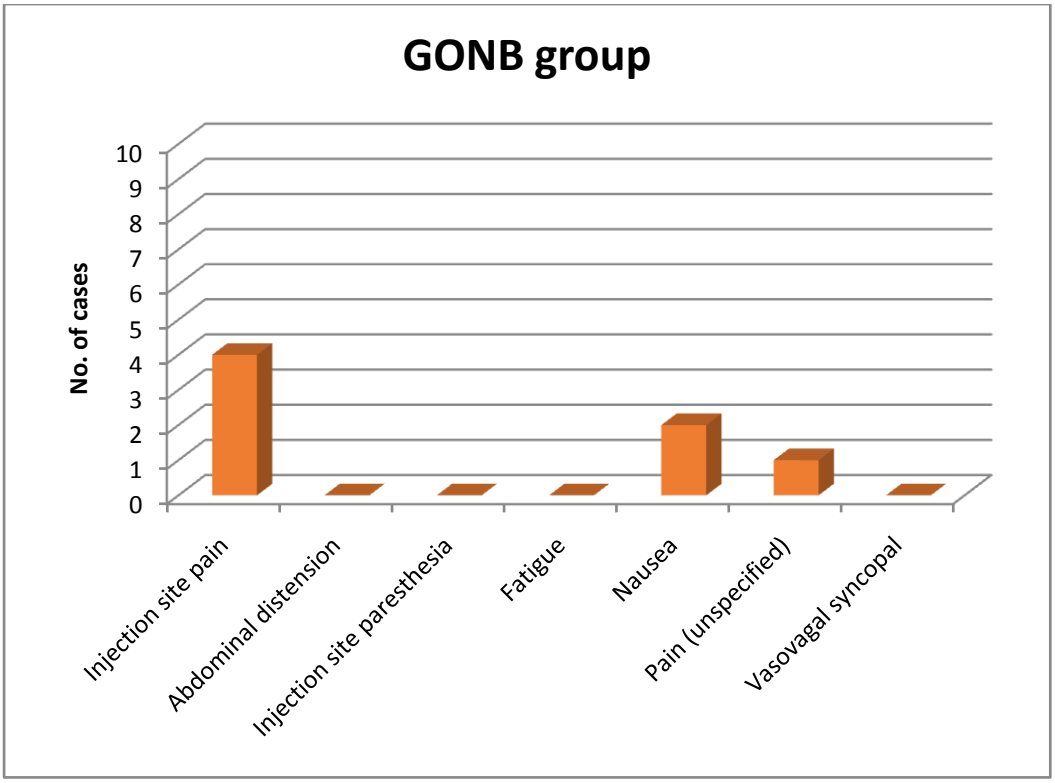


Figure 14. Adverse events in GONB group.

Discussion

Migraine headaches represent a common and extremely debilitating neurologic disorder that was recently classified as the third most common cause of disability worldwide.[1]Migraine is characterized by a combination of headache with one or more other neurological, gastrointestinal, and autonomic symptoms. Although migraine is a highly prevalent and disabling condition, it is under-diagnosed and under-treated.

Chronic migraine (CM) is diagnosed when headaches occur on 15 days or more per month for at least 3 months of which at least 8 days or more with headaches are associated with migraine. There is severe reduction in performance of patients, quality of life, family and social activities, in addition to the work or school being affected.[48]

Recent advances have been made in the management of migraine, but pharmacologic treatment options are still far from optimum, leaving many patients without pain-free treatment or with unpleasant side effects. Patients with frequent, disabling, or refractory migraine are candidates for prophylactic treatment. Available therapies for the prevention of migraines are often associated with adverse effects. Treatment options for migraine have been historically limited to pharmaceutical agents or cognitive behavioural therapy and more recently the use of botulinum toxin or corticosteroid induced nerve block. Injections of BOTOX and GONB are generally well tolerated, with no significant adverse events.

Botulinum toxin type A (BoNT-A) is a potent neurotoxin and its pain-relieving effects were initially noted in studies of the treatment of cervical dystonia, and several studies subsequently showed that the toxin may be effective in the treatment chronic migraine. GON blockade with local anaesthetics is an effective treatment for a group of headaches, such as cervicogenic headache, cluster headache,

occipital neuralgia, migraine. In our study, we aimed to assess the safety and efficacy of both the modes in chronic migraine patients

A total of 20 number of patients were enrolled in our study, 4 patients participated in botulinum toxin injection group and 16 patients participated in greater occipital nerve block. The number of cases were less because of the on-going pandemic which significantly affected the outpatient department.

Patients were explained about the method of administration and safety profile of both BOTOX and GONB and they were free to choose between the GONB and BOTOX intervention, but more number of patients opted for GONB because of cost effectiveness and less number of injection sites.The use of any concurrent medication was recorded along with the reason the medication was taken at the baseline and during the study.

The mean age of the patients in our study was 42±10.24 years in both groups, which is similar to the study done by Ahmed et al, who found the mean age as 45.4 ± 11.7 years and Blumenfeld et al who found the mean age to be 43 years [85,88]. Ulusoy et al and Vigano et al, however reported a slightly lower mean age group of 36.1 ± 7.8 years, and 32.9 ± 14.5 years, respectively. [86,87]

The mean headache duration was 13±5.75 years in our study, which was slightly more than the duration of 10.6 years reported by Blumenfeld et al[88] in their study but less than the duration of 20 (10.8–25.3) years observed by Cuadrado et al[89] in their study.

In our study, we saw female preponderance in the study subjects as13 out of 16 (81.25%) in GONB group and 4 out of 4 in BOTOX group. Chronic migraine itself is female predominant and it was consistent with most of the studies.This finding was similar to the studies done by Blumenfeld et al [88], which included 85% females, Ulusoy et al [86], which included 85.7% females, Ahmed et al [85] included 85.3% females

and Gul et al[81], had 86.3% females, Inan et al [83] included 93.9% females.

The area of headache involved in patients receiving Botox injection was left hemicranial area in 50% patients, while 44% of chronic migraine patients receiving GONB injection reported to have holocranial headache. In the study done by Blumenfeld et al [84], 46.6% patients complained of headache on both sides of head, while Inan et al[83] in their study reported that 45.5% patients had bilateral headache.

In our study, the number of headache days prior to Botox injection in last 4 weeks were 26 days, similar to what Blumenfeld et al [88] in their study observed 22.0 ± 4.8 headache days in the last month before injection. Dilli et al [90], in their study, observed that the baseline frequency of days with moderate or severe migraine headache ranged from one to 24 days per 28-day period, with a mean of 9.6 ±4.8 days.

Analyses of Efficacy

In our study, in the last 4 weeks prior to the Botox injection, on an average, the patients complained of 26 days of headache while after the injection, the mean duration reduced to 12 headache days. Similarly, Ahmed et al [85] in their study found that at baseline, the mean (SD) headache-day frequency was 20.6 ±5.4, which reduced to 7.4±6.6 at administration visit 8. Blumenfeld et al [88] also observed that the mean headache days reduced to 11.3±7.4 days per 28-day period from 22.0±4.8 days. Young et al[77]observed that while the baseline mean headache days in the last 4 weeks were 20.3±4.0, it reduced to 11.8±6.9 post the Botox injection.

The headache free days were less in the initial weeks in the BOTOX group and as the time passed by the headache free days improved in the latter week.

In the GONB group, the patients had an average number of 22.63 headache days prior to the injection in the last 4 weeks, while after the injection, it reduced to 10.81 mean headache days. Similar findings were observed by Gul et al[81] in their study, where the mean headache days reduced from 21.0±4.4 pre-treatment to 10.9±7.1 in the first month post injection. Inan et al [83] also reported a reduction in the number of headache free days from 16.9 ±5.7 pre-treatment to 8.4 ± 5.0 in the 2nd month post GONB injection.

The headache free days were more in the initial weeks in the GONB group and as the time passed by the headache free days declined in the latter weeksx.

Prior to the Botox injection, among the 4 patients, the mean headache severity in terms of Visual Analog Scale was in the range 4-7 for 2 patients, while it was severe (7-10) for 2 patients. After the Botox Injection, we compared the number of headache days on the basis of severity. It was observed that the number of headache days with higher severity reduced. The patients had 7 mean headache days with severity 0-4, while they had 3.75 mean headache days with severity 4-7 and only 1.5 mean headache days with severity 7-10 on the Visual Analog Scale**.**

Young et al [77] in their study considered other parameters (HIT6 and MIDAS) but they had similar observations. Onabotulinum toxin A significantly reduced the mean HIT-6 total scores from a baseline of 65.6 ±5.2 and 64.6 ±4.6 in patients with and without daily headache at baseline, respectively, to 60.9 ±7.1and 58.6 ±6.8 for the 28-day period before week 24; to 59.6 ±6.7 and 56.8±7.1 at week 60; and to 55.9 ±7.7 and 55.3±7.5 at week 108 (all $P < 0.001$ for within-group comparison with baseline). Onabotulinum toxin A significantly reduced mean MIDAS total scores in patients with and without daily headache from a baseline score of 90.6 ±66.3 and 73.3±53.4, respectively, to 63.7 ±66.3 and 35.5 ±43.3 at week 24; to 56.2 ±68.2 and 25.4 ±30.8 at week 60; and to 41.9.

Blumenfeld et al[88], in their study compared the HIT-6 scores of the participants, and observed statistically significant improvements in total HIT-6 at week 12 (HIT-6 score reduced by 4.4 points from baseline; P < 0.0001) and continued through to week 108 (− 7.1 from baseline; P < 0.0001). A similar pattern was seen using observed data (week 12: − 4.4 from baseline; week 108: − 9.0 from baseline; both P < 0.0001). At baseline, patients had a mean of 18.0±5.7 moderate or severe headache days. The frequency of moderate or severe headache days was reduced from baseline by 6.5 days at week 24, a statistically significant change from baseline (P < 0.0001). The reduction in moderate or severe headache days remained significantly reduced compared with baseline at week 60 (− 8.1 days; P < 0.0001) and at week 108 (− 9.5 days; P < 0.0001).

Ahmed et al [85] in their study considered the EuroQol 5-Dimension Questionnaire (EQ-5D). Statistically significant (P < 0.001) improvement was observed in the EQ-5D total score as early as administration visits 2 through 8. At administration visit 8, the median EQ-5D total score change from baseline was 0.20 (P<0.001), from a median baseline score of 0.69. Similarly, statistically significant (P < 0.001) changes from baseline were observed in health state score at administration visit 2 through administration visit 8. At administration visit 8, the health state score median change from baseline was 20.0 (P < 0.001), from a median baseline score of 50.0.

Prior to the GONB injection, among the 16 patients who received it, 8 had a mean headache severity in the range 7-10, while 6 patients had a severity range of 4-7 and 2 had a severity range of 0-4.

Gul et al[81] in their study also observed a reduction in the VAS scores from baseline in patients who received GONB injection. While the pre-treatment score in their study was 8.9±0.8, it reduced to 5.6 ± 3.0 in the first month post injection. This gradual decrease continued until the second week. After the second week in the treatment group, this reduction continued and VAS score reached 0.97 at the end of the

fourth week. After the second week, in the placebo group, VAS score increased again and nearly reached the pre-injection levels. Dilli et al [90], in their study observed that the percentage of patients with at least 50% reduction in the frequency of moderate or severe migraine headache was 30% (10/33, p= 0.00, 95% CI –0.22 to 0.23). Similarly, Palamar et al[82] in their study observed that the pre-treatment VAS was 3.93±1.80 which reduced to 1.55±1.42 post the GONB injection. This decrease on the injected side in the treatment group was found to be statistically significant (*P* = 0.003). The pain intensity decreased to 2.16 in the first week after the injection, and this decline continued during the subsequent weeks.

Most of the studies showed that GON blockade is effective in migraine, including placebo-controlled studies and even though GONB and BOTOX has demonstrated favourable results in clinical practice, until recently, little evidence existed in the literature for its efficacy in the treatment of migraine headaches. In our study we did not compare the two groups, we individually assessed the efficacy of BOTOX and GONB on the basis of number of headache days and severity of headache according to VAS, before and after the intervention and both the groups were efficacious in declining the number of headache days as well as the headache severity. No injection was repeated in any of the group, although the follow up period in our study was 4 weeks but the patients are still being followed up and 50% patient in the BOTOX group were willing for a repeat injection as compared to 31% in the GONB group after a mean of 10 weeks.

Safety and Tolerability.

Adverse events during follow-up were assessed for all 20 patients in the Botox and GONB group. No serious adverse events were reported in the both the groups. A relatively few adverse effects, however were reported. Injection site pain lasting <24 hours was noted in one patient and one patient observed fatigue for 5 days post intervention in the Botox group.

We compared this with other studies where Botox Injection was given for chronic migraine. Ahmed et al[85]in their study observed that only 18.3% reported adverse effects. Out of these, 7.1% reported mild to moderate adverse effects while 3.8% reported severe adverse effects. ADRs in >2% of patients were eyelid ptosis (5.4%), neck pain (2.8%), and musculoskeletal stiffness (2.7%). Blumenfeld et al [88]reported a few adverse effects, in around 18.3% of the total patients enrolled. These included eyelid ptosis and rash, 0.4% each. Young et al[77] in their study, observed that AEs occurred in 14.5% patients with daily headache and 8.7% without daily headache.

Injection site pain lasting <1 hour was noted in four patients following the injection in the GONB group. There was no statistically significant difference in adverse events between the Botox and GONB groups. Gul et al [81] in their study, administered GONB injection. No serious adverse effect was observed. Local pain at the site of injection, vertigo, and nausea were reported in some patients, but all the patients had completed the treatment sessions.

In the study done by Dilli et al [90], no serious adverse events were reported in the active group. Injection site pain was observed in 12% patients receiving GONB.

LIMITATIONS OF OUR STUDY

The flaws inherent in our methodology obviously limit what conclusions may be drawn from our results.

1. The study was unblinded and lacked any control therapy, active or placebo.
2. Sample size of subjects (BOTOX and GONB group) was less in our study due to on-going COVID-19 pandemic situation.
3. There was a high female preponderance in both BOTOX group and GONB group.
4. Cost-effectiveness of treatment with onabotulinum toxin-A was an important issue for patients.
5. The data utilized for analysing the primary outcome variable were partially dependent upon patient recall, and recall bias and could have inflated the response rate.

Summary and Conclusion

Summary

- The aim of our study was to demonstrate safety and efficacy of administration of greater occipital nerve block and botulinum toxin A in patients with chronic migraine.
- Onabotulinum toxin was administered according to PREEMPT protocol with 31 small injections of 5 units each placed at prescribed locations over the forehead, sides of the head, and back of the head and neck.
- Greater occipital nerve block was given by preparing a mixture of 3 mL of 2% lidocaine and 80 mg of methylprednisolone. The preparation is given by a 22-gauge needle which is advanced beneath the lateral border of the probe using real-time ultrasound guidance and an in-plane technique.
- A total of 20 eligible patients consented to participate (4 onabotulinum toxin type A injection and 16 greater occipital nerve block)
- Among the patients who received Botox Injection, all were females, and the mean age was 42.25 years (range 33-55 years). The patients complained of a mean headache duration of 13.00 years (range 7-20 years)
- Among the patients who received GONB, the mean age was 42.13 years (range 24-74 years) and 13 patients were female (81.3%). The patients complained of a mean headache duration was 13.44 years (range 1-40 years).
- Among the patients who received Botox Injection the baseline frequency of days with migrainous headache ranged from 20 to 28 days per 28-day period, with a mean of 26.00 days (SD 4.0).
- Among the patients who received GONB the baseline frequency of days with migrainous headache ranged from 15 to 28 days per 28-day period, with a mean of 22.63 days (SD 5.1).

- In the last 4 weeks prior to the Botox injection, on an average, the patients complained of 26 days of headache while after the injection, the mean duration reduced to 12 headache days.
- Four weeks post the BOTOX injection, patients reported a mean of 15.75 headache free days.
- The GONB group, the patients had an average number of 22.63 headache days prior to the injection in the last 4 weeks, while after the injection, it reduced to 10.81 mean headache days.
- Four weeks post the GONB injection, the mean headache free days reduced to 17.19.
- Prior to Botox injection, among the 4 patients, the mean headache severity in terms of Visual Analog Scale was in the range 4-7 for 2 patients, while it was severe 7-10 for 2 patients and after the injection patients had 7 mean headache days with severity 0-4, while they had 3.75 mean headache days with severity 4-7 and only 1.5 mean headache days with severity 7-10 on the Visual Analog Scale.
- Prior to the GONB injection, among the 16 patients who received it, 8 had a mean headache severity in the range 7-10, while 6 patients had a severity range of 4-7 and 2 had a severity range of 0-4 and after the injection the patients had 7.31 mean headache days with severity 0-4, they had 2.63 mean headache days with severity 4-7 and only 0.88 mean headache days with severity 7-10 on the Visual Analog Scale.
- No serious adverse events were reported in the both the groups, however a relatively few adverse effects were reported

Conclusion

Chronic migraine remains a leading cause of disability globally. In the setting of inadequate treatment responses to medical prophylactic interventions, the search for the effective treatments for chronic migraine is still on-going.

Patients with frequent, disabling, or refractory migraine are candidates for prophylactic treatment. Available therapies for the prevention of migraines are often associated with adverse effects. Injections of BOTOX and GONB are generally well tolerated, with no significant adverse events. Accumulating anatomic research and the effectiveness and increasing use of peripherally- and even extracranially- directed treatments speaks to the growing acceptance of the role of peripheral structures in the development of headache.

Chronic migraine treatment with onabotulinumtoxinA and GONB was associated with a reduction in monthly headache days and decreased headache severity (according to VAS scale); though the sample size is small but the data support the safety and efficacy for the use of onabotulinumtoxinA for the treatment of chronic migraine in clinical practice.

These intervention seems to be the most reliable path for the transitional treatment of refractory chronic migraine in order to take them back toward non-refractoriness, which can be easily treated by the conventionally-accepted preventive therapies.

Aside from the fact that there are limited therapeutic options available, the obvious advantages of BOTOX and GONB for suppression of chronic migraine include the ease with which the procedure may be performed, its relative safety, and the potential removal of the need to administer oral prophylactic therapy on a daily basis.

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S no	MRD	Age	Sex	Area involved	Triggers	Headache duration	Headache days prior to injection in last 4 weeks	Headache free days prior to injection	Mean headache severity prior to injection (visual analog scale)	Analgesic use prior to injection	Headache days after injection
1	1092019	55	female	Holocranial	Travelling, sleep deprivation	20years	28	0	4-7	30 tab naxdom	17
2	917570	46	female	Left Hemicranial	Travelling, sleep deprivation, stress	15years	28	0	7-10	20tab (naxdom,combiflam,rizact)	14
3	1010411	35	female	Right hemicranial	Travelling, sleep deprivation, stress,fasting	10years	20	8	7-10	10tab rizact	5
4	1171630	33	female	Left Hemicranial	Stress,fasting	7years	28	0	4-7	14tab Naxdom	13

S no	MRD	Headache days with severity 0-4 (visual analog scale) after injection	Headache days with severity 4-7 (visual analog scale) after injection	Headache days with severity 7-10 (visual analog scale) after injection	Severity (visual analog scale) on maximum days	Response	Analgesic use after injection	Headache free days in week 1	Headache free days in week 2	Headache free days in week 3	Headache free days in week 4	Headache free days after 4 weeks
1	1092019	8	7	2	0-4	partial	5days 3d naxdom 2d rizact	1	1	4	5	11
2	917570	10	2	2	0-4	partial	3days (naxdom)	2	3	4	5	14
3	1010411	5	0	0	0-4	partial	0days	4	6	5	8	23
4	1171630	5	6	2	4-7	partial	07days naxdom	2	3	5	5	15

S no	MRD	Age	Sex	Area involved	Triggers	Headache duration	Headache days prior to injection in last 4 weeks	Headache free days prior to injection	Mean headache severity prior to injection (visual analog scale)	Analgesic use prior to injection	Headache days after injection
1	1138162	30	male	holocranial	Travelling, sleep deprivation	10years	16	12	4-7	10tab disprin naxdom	15
2	1145257	44	female	Right hemicranial	Stress, sleep deprivation, weather change	15years	28	0	7-10	20tab rizact naxdom	10
3	917570	45	female	Left hemicranial	Sleep deprivation	20years	28	0	0-4	3 tab disprin	20
4	1135397	43	female	Left hemicranial	Travelling, fasting	10years	28	0	4-7	10tab combiflam	13
5	1146176	33	female	Right hemicranial	Travelling, sleep deprivation, weather change	5 years	20	8	7-10	10tab (sumo)	14
6	1168138	50	female	holocranial	Travelling	20years	20	8	0-4	-	20
7	1169566	32	female	holocranial	Travelling, sleep deprivation	06 years	20	8	4-7	20 tab (naxdom)	5
8	810272	26	female	holocranial	Travelling, sleep deprivation, fasting,stress	2 years	20	8	4-7	10tab (indocap sr)	7
9	843473	52	male	Left hemicranial	Fasting	20years	28	0	7-10	20tab combiflam	6
10	751612	28	female	Left hemicranial	-	4 years	28	0	4-7	20 tab(rizact, brufen)	10
11	1084492	24	female	Right hemicranial	Travelling, sleep deprivation, stress	2 years	20	8	4-7	10 tabs dolo 650	2
12	1092019	55	female	holocranial	Travelling, sleep deprivation	20years	28	0	7-10	60-90 tab rizact	23
13	146759	74	female	occipital	-	40years	15	13	7-10	10tab (crocin,pcm)	2
14	132777	67	male	holocranial	weather change	30years	20	8	7-10	05tab (combiflam,naxdom)	8
15	812092	45	female	Right hemicranial	Sleep deprivation,fasting	10years	15	13	7-10	3 tab (pcm)	11
16	928840	26	female	holocranial	Sleep deprivation,fasting	1 year	28	0	7-10	10tab combiflam	7

S no	MRD	Headache days with severity 0-4 (visual analog scale) after injection	Headache days with severity 4-7 (visual analog scale) after injection	Headache days with severity 7-10 (visual analog scale) after injection	Severity (visual analog scale) on maximum days	Response	Analgesic use after injection	Headache free days in week 1	Headache free days in week 2	Headache free days in week 3	Headache free days in week 4	Headache free days after 4 weeks
1	1138162	10	5	0	0-4	partial	06days (naxdom)	6	4	3	0	13
2	1145257	3	5	2	4-7	partial	04 days (naxdom)	5	5	4	4	18
3	917570	20	0	0	0-4	partial	0 days	4	2	1	1	8
4	1135397	7	6	0	0-4	partial	04 days combiflam	6	4	3	2	15
5	1146176	5	7	2	4-7	partial	02 days naxdom	7	3	3	1	14
6	1168138	20	0	0	0-4	partial	-	4	2	1	1	8
7	1169566	5	0	0	0-4	partial	-	7	7	6	3	23
8	810272	5	2	0	0-4	partial	02 days naxdom	6	6	5	4	21
9	843473	2	2	2	0-4	partial	-	6	6	5	5	22
10	751612	5	3	2	0-4	partial	05 days naxdom	6	5	4	3	18
11	1084492	2	0	0	0-4	partial	-	7	7	7	5	26
12	1092019	20	3	0	0-4	partial	naxdom 20 tabs	2	1	1	1	5
13	146759	0	2	0	4-7	partial	-	7	7	7	5	26
14	132777	4	2	2	0-4	partial	-	7	6	5	2	20
15	812092	5	2	4	0-4	partial	-	6	5	4	2	17
16	928840	4	3	0	0-4	partial	-	7	5	5	4	21

Name of the examinee DR. RAJIV KU...

Baba Farid University
of Health Sciences
Sadiq Road
Faridkot-151 203 (Pb). INDIA.
Phone : 01639-256232,256236
Tele/Fax : 01639-256235
Email – Examination@bfuhs.ac.in

No. BFUHS/2K21p-TH/ 11463

Date 4/2/2021

The Principal,
DMC, Ludhiana

Subject: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 22.01.2021 has approved the plan of thesis of Dr Balveen Singh, a student of your college for DM Neurology along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Evaluation of botulinum toxin a and greater occipital nerve block in treatment of chronic migraine

Supervisor
Dr. Gagandeep Singh
Prof. & Head,
Dept. of Neurology,
DMCH, Ludhiana.

Co-Supervisor
Dr. Monika Singla
Assoc. Prof.,
Dept. of Neurology,
DMCH, Ludhiana.

The student has to submit the three copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, If he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

Dr. S P Singh MS(Opth)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

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8/1/22

Baba Farid University of Health Sciences
Sadiq Road, Faridkot (Punjab) India
Phone No.01639-256232, 36 (Reception)
Fax No.01639-256234, 256235 (Exams.)
E-Mail: bfuhsthesis@gmail.com

No. 07-BFUHS/Exam/2022/ 21 Date: 4/1/2022

The Principal,
DMC, Ludhiana.

Subject: **Regarding:** - Regarding Extension - Dr. Balveen Singh, DM Neurology.

This is with reference to your office letter no DMCH/P/2021/9 dated 28.12.2021 & subject mentioned above, you are hereby informed that the competent authority after going through your request has very kindly allowed for extension in duration in participant's selection which is till October, 31, 2021. You are further requested to attach this letter in the thesis also.

Dr. S.P.Singh MS(Oph)
Controller of Examinations

EVALUATION OF BOTULINUM TOXIN A AND GREATER OCCIPITAL NERVE BLOCK IN TREATMENT OF CHRONIC MIGRAINE

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

IN

NEUROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

FEBRUARY, 2020

DR. BALVEEN SINGH

DEPARTMENT OF NEUROLOGY

DAYANAND MEDICAL COLLEGE & HOSPITAL

LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	Evaluation of Botulinum Toxin A and Greater Occipital Nerve block in treatment of chronic migraine
For the degree of	D.M Neurology
Name of the candidate	Dr. Balveen Singh
Supervisor	Dr. Gagandeep Singh, Professor & Head, Department of Neurology, DMCH, Ludhiana
Co-supervisor	Dr. Monika Singla, Associate Professor, Department of Neurology, DMCH, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Migraine is a common disabling primary headache disorder. Chronic migraine, defined as headaches on ≥15 days per month for ≥3 months, of which ≥8 days meet criteria for migraine without aura or respond to migraine-specific treatment, is estimated to affect 2% of the population. It results in substantial disability and reduced quality of life (QoL) and leads to an increased risk of anxiety and depression therefore the efficacy of Greater occipital nerve block and Botulinum toxin A in patients with adult chronic migraine needs to be studied in detail.

Aim of Study: Our aim is to demonstrate safety of administration and efficacy of Greater occipital nerve block and Botulinum toxin A in patients with adult chronic migraine.

Materials & Methods: A non-randomized prospective observational study will be conducted on adult patients with chronic migraine (defined according to the 2018 International Headache Society Criteria), patients will be offered Botulinum toxin A or Greater Occipital Nerve block after discussion of all available treatment options. Patients will be followed for 30 days and a headache diary will be used to evaluate the frequency and intensity of headache in chronic migraine patients receiving any one of the two modalities. All follow up and new patient's presenting to DMCH Ludhiana from March 2020 to October, 31, 2021 will be enrolled for study after taking informed and written consent.

Clinical Significance: This study will help us to find out the safety of administration and efficacy of Greater occipital nerve block and Botulinum toxin A in patients with adult chronic migraine.

Keywords: Chronic migraine, Greater Occipital Nerve block, Botulinum toxin A

(Signature) Candidate | (Signature) Co-supervisor | (Signature) Supervisor | (Signature) Principal

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CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"EVALUATION OF BOTULINUM TOXIN A AND GREATER OCCIPITAL NERVE BLOCK IN TREATMENT OF CHRONIC MIGRAINE"** exist in the Department of Neurology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself/herself under our supervision and guidance.

Supervisor

Dr. Gagandeep Singh
Professor & Head
Department of Neurology
DMCH, Ludhiana

Co-Supervisors

Dr. Monika Singla
Associate Professor
Department of Neurology
DMCH, Ludhiana

Head of the Department

Dr. Gagandeep Singh
Professor & Head
Department of Neurology
DMCH, Ludhiana

Place: _____

Date: _____

APPROVAL PROFORMA
BY RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Balveen Singh
Department	Neurology
Topic of Thesis	Evaluation of Botulinum Toxin A and Greater Occipital Nerve block in treatment of chronic migraine
Likely date of appearing in PG examination	MAY, 2022
Date of enrollment	10th September 2019
Name of Head of Department	Dr. Gagandeep Singh
1) Supervisor **2) Co-Supervisor(s)**	Dr. Gagandeep Singh Dr. Monika Singla
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Jaspal Singh (Professor & Head, Surgery)	Mr. A K Jindal (Member, Ethics Committee)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
Dr. Sandeep Kaushal (Assistant Dean Academics)	Dr. Deepinder K Chhina (Professor & Head, Microbiology)
Dr. Rajoo Singh Chhina (Dean Academics)	Dr. Neena Sood (Professor & Head, Pathology)
Dr. Gurpreet S Wander (Vice Principal)	Dr. Gurpreet S Wander (Vice Principal)
	Dr. Gagandeep Singh (Secretary, Ethics Committee Professor & Head, Neurology)

Approved: Yes / ~~No~~

Dr. Sandeep Puri
Chairperson
Research Committee
Chairperson
Research Committee

Approved: Yes / ~~No~~

Prof. Arvind Malhotra
Chairperson
Ethics Committee
Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Dr. Balveen Singh
2	NAME OF THE INSTITUTE	DAYANAND MEDICAL COLLEGE AND HOSPITAL LUDHIANA
3	COURSE OF STUDY AND SUBJECT	DM NEUROLOGY
4	DATE OF ADMISSION OF COURSE	10th September 2019
5	TITLE OF THE TOPIC	EVALUATION OF BOTULINUM TOXIN A AND GREATER OCCIPITAL NERVE BLOCK IN TREATMENT OF CHRONIC MIGRAINE

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Chronic daily headache (CDH) is a broad term, which includes groups of headache disorders, and it is not a diagnosis. “The term chronic daily headache is applied when the headache frequency is ≥15days a month for ≥3 months.[1]

Migraine is a common disabling primary headache disorder. Many epidemiological studies have documented its high prevalence and socio-economic and personal impacts. In the Global Burden of Disease Study 2010 (GBD2010), it was ranked as the third most prevalent disorder in the world. In GBD2015, it was ranked the third-highest cause of disability worldwide in both males and females under the age of 50 years.[2]

Chronic migraine, defined as headaches on ≥15 days per month for ≥3 months, of which ≥8 days meet criteria for migraine without aura or respond to migraine-specific treatment.[2]

Patients with chronic migraine are more likely to use healthcare resources than those with episodic migraine (defined as migraine and <15 headache days per month) [2], and one in five chronic migraine sufferers cannot work due to the effect of the condition on their ability to lead a productive life.[3] Chronic migraine sufferers are also significantly more likely to re- port depression, anxiety, chronic pain and respiratory disorders than non-chronic migraine sufferers.[4]

Medications used for prophylaxis in episodic migraine may also work in chronic migraine, although only topiramate has established evidence.[5,6] However, this and other unlicensed oral agents have limitations due to poor tolerability and/or adverse effects, and a considerable number of patients do not respond.[7,8]

Observational and clinical trials have shown that 50-80% of patients with chronic migraine overuse acute medication.[9] As to whether the two are separate entities or a complication of one another remains uncertain.[10]

Therefore for patients who fail on oral therapies, there is also now the option of treatment with Onabotulinum toxin A and greater occipital

nerve block, so in this study we would like to study the efficacy, safety and adverse outcomes with use of Onabotulinum toxin A and greater occipital nerve block

6.2 REVIEW OF LITERATURE

Migraine has two major types:

1.1 Migraine without aura

1.2 Migraine with aura

1.1 Migraine without aura

Diagnostic criteria:

A. At least five attacks fulfilling criteria B–D

B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:

- Unilateral location
- Pulsating quality
- Moderate or severe pain intensity
- Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:

- Nausea and/or vomiting
- Photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

1.2 Migraine with aura

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:

- Visual
- Sensory
- Speech and/or language
- Motor
- Brainstem
- Retinal

C. At least three of the following six characteristics:

- At least one aura symptom spreads gradually over 5 minutes

Two or more aura symptoms occur in succession

Each individual aura symptom lasts 5–60 minutes

At least one aura symptom is unilateral

At least one aura symptom is positive

The aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis.

1.3 Chronic migraine

Description: Headache occurring on 15 or more days/ month for more than three months, which, on at least eight days/month, has the features of migraine headache.

Diagnostic criteria:

A. Headache (migraine-like or tension-type-like) on 15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 Migraine with- out aura and/or criteria B and C for 1.2 Migraine with aura

C. On 8 days/month for >3 months, fulfilling any of the following:

a. Criteria C and D for 1.1 Migraine without aura

b. Criteria B and C for 1.2 Migraine with aura

c. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.

Silberstein *et al*. 2000 showed that as compared with vehicle treatment, subjects in the 25-U botulinum toxin type A treatment group had significantly fewer migraine attacks per month, a reduced maximum severity of migraines, a reduced number of days using acute migraine medications, and reduced incidence of migraine-associated vomiting. Both the 25-U and 75-U botulinum toxin type A groups were significantly better than the vehicle group on subject global assessment. Botulinum toxin A treatment was well tolerated, with only the 75-U treatment group exhibiting a significantly higher rate of

treatment-related adverse events than vehicle.[11]

In a randomized, placebo-controlled, parallel design study by **Ondo *et al*. 2004** sixty patients with headaches of more than 15 days per month were recruited for this double-blind, placebo-controlled, parallel study of botulinum toxin type A (BTX) for chronic tension type and chronic migraine headaches. Over a 12-week period after injections, headache-free days had improved in the BTX group from week 8 to 12 ($P < 0.05$), and strongly tended to improve over the entire 12-week period, 33 ± 23 vs. 24 ± 16 days without headache ($P = 0.07$), but did not meet the *a priori* significance criteria. The subject global impressions ($P < 0.05$), subject change in headache impressions ($P<0.005$), and investigator global impressions ($P<0.001$) all improved in the BTX group compared with placebo.[12]

David W. Dodick et al randomized a total of 1384 adults to onabotulinumtoxin A (n = 688) or placebo (n = 696). Pooled analyses demonstrated a large mean decrease from baseline in frequency of headache days, with statistically significant between-group differences favoring onabotulinumtoxin A over placebo at week 24 (-8.4 vs -6.6; $P < .001$) and at all other time points. Significant differences favoring onabotulinumtoxin A were also observed for all secondary efficacy variables at all time points, with the exception of frequency of acute headache pain medication intakes. Adverse events occurred in 62.4% of onabotulinumtoxin A patients and 51.7% of placebo patients. Most patients reported adverse events that were mild to moderate in severity and few discontinued (onabotulinumtoxin A, 3.8%; placebo, 1.2%) due to adverse events. No unexpected treatment-related adverse events were identified.[13]

Vo *et al*. in 2007, a small, but double-blinded and placebo-controlled study with 32 participants failed to demonstrate a benefit for onabotulinumtoxinA in the prophylactic treatment of CM.[14]

Sandrini *et al*. 2011 An Italian double- blind study with 68 patients with CM found no difference between onabotulinumtoxinA and placebo in the reduction of headache days, but was able to show, that treatment with onabotulinum- toxin A reduced the consumption of acute pain

medication.[15]

The breakthrough of onabotulinumtoxinA in the treatment of CM came in 2010, when the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) study group published the results of the PREEMPT I and PREEMPT II trial, in which a total of 1384 Patients were enrolled into both trials (PREEMPT I: 679, PREEMPT II: 705). Both studies consisted of a 28-day baseline screening period, a 24-week double-blind, parallel-group, placebo-controlled phase (two injection cycles) and a 32-week open- label phase (three injection cycles). This pair of two multicentre randomized, placebo-controlled studies had an identical study design, but different endpoints.

In the PREEMPT I trial the primary endpoint reduction of migraine episodes was missed, but significant differences between the *verum* group and the placebo group were seen in the reduction of headache days and migraine days [**Aurora *et al*. 2010**].[16] The PREEMPT II trial confirmed the effi- cacy of onabotulinumtoxinA in the reduction of headache days as a primary endpoint [**Diener *et al*. 2010**].[17]

The positive results of the two PREEMPT trials led to the approval of onabotulinumtoxinA for the treatment of CM in September 2011 by the US FDA and subsequently many other registration authorities worldwide.

Ashkenazi and Young [18] Performed a prospective, non-controlled study to look at the effect of GON block on head pain and allodynia in a cohort of 19 patients with migraine. Both local anesthetic and steroids were used. They noted a significant improvement after the procedure, with 90% of the group documenting relief from head pain An RCT by Ashkenazi et al. compared the effect of local anesthetic mixture (lidocaine 2% þ bupivacaine 0.5%) with or without 40 mg triamcinolone. Both bilateral GON block and trigger point injections (TPI) to cervical paraspinal and trapezius muscles were per- formed. Mean duration of headache, mean analgesic consumption, and the mean duration of being head- ache-free did not differ significantly between the two treatment groups at the end of the fourth week ($p < 0.05$). GON block and TPIs were effective; the addition of triamcinolone was useless.

Cuadrado et al [19], included 36 patients with chronic migraine treated with bilateral GON block with bupivacaine (n 18) or a sham procedure with normal saline (n 18). Anesthetic block was superior to placebo in reducing the frequency of headaches during the week after injection, along with an increase in pressure pain thresholds in various territories.

Dilli and colleagues compared 0.25mL 1% lidocaine (placebo) to a mixture of 2.5 mL 0.5% bupivacaine and 20 mg methylpredniso-lone.[20] They reported that there was no difference in response rate, defined as at least a 50% reduction in the frequency of moderate or severe migraine headache days after the intervention. They also stated that migraine duration, acute analgesic consumption, and mean migraine frequency did not differ statistically in each group.

RCT that was undertaken by **I–nan et al.** compared GON block with 1.5 mL bupivacaine 0.5%, and 1mL saline (treatment) and GON block with 2.5mL saline (placebo).[21] GON blocks were applied weekly for a month. Mean headache duration reduced in the treatment group after the first month ($p < 0.001$), while the placebo group experienced no reduction (p1⁄40.223). After blinding was removed, there was no difference between groups in the second and third months. A mean headache day reduced in both groups, but this reduction was significant in the treatment group. VAS decreased in both groups after the first month, but the VAS decrease was more significant in the treatment group.

6.3 AIMS AND OBJECTIVES OF THE STUDY

Our aim is to demonstrate safety of administration and efficacy of Greater occipital nerve block and Botulinum toxin A in patients with chronic migraine.

7.0 MATERIALS AND METHODS

This prospective, observational and non-blinded study will be conducted to know the efficacy, safety and adverse effects of Botulinum toxin and greater occipital nerve block in patients with chronic migraine.

7.1 SOURCE OF DATA

Data collection will be done from all follow up and new patients presenting with chronic migraine (defined according to the 2018 International Classification of headache disorder ICHD-3) participating in Botulinum toxin or greater occipital nerve block to DMCH Ludhiana from March 2020 to October, 31, 2021 after taking informed and written consent.

7.2 METHOD OF COLLECTION OF DATA

Inclusion Criteria

Patient who present to DMCH/HDHI in patient/ out patient clinic:

1. Age ≥ 18 years and ≤ 80 years
2. Adult with chronic migraine (defined according to the 2018 International Classification of headache disorder ICHD-3)

Exclusion criteria

1. Age < 18 years
2. Patients who have intracranial space occupying lesion
3. Patients with a concomitant medical illness such as end-stage organ failures e.g. renal, cardiac, hepatic, respiratory, secondary causes of CDH
4. Pregnant females

OUTCOME: The efficacy, safety and adverse effects of Botulinum toxin and greater occipital nerve block in patients with chronic migraine would be known by this study.

STATISTICAL ANALYSIS: Data will be described in terms of range; mean ±standard deviation (± SD, frequencies (number of cases) and relative frequencies (percentages) as appropriate. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

GREATER OCCIPITAL NERVE BLOCK

The greater occipital nerve (GON) originates in the dorsal ramus of the C_2 as well as the C_3 segments of the spinal cord and comprises sensory fibers alone. Its sensory distribution path- way includes the posterior part of the head and extends anteriorly toward the vertex, becoming superficial at the infero lateral aspect of the occipital protuberance. It is thought that sensory input from the GON and the ophthalmic branch of the trigeminal nerve converges into the trigeminal nucleus caudalis, which is hypothesized to be the reason why occipital neuralgia is sometimes associated with migraine headache symptomatology. GON block decreases afferent input to the trigeminal nucleus caudalis, resulting in central pain modulation and reducing neuronal hyper excitability at the level of second-order neurons. The procedure to inject the GON involves inserting a needle into the infero lateral aspect of the occipital protuberance and injecting a combination of local anesthetic and a corticosteroid.

Onabotulinumtoxin A

The PREEMPT protocol for onabot injections is the only FDA-approved injection pattern for chronic migraine, and practitioners are specially trained in its administration. Although cosmetic onabot is chemically identical to that used for chronic migraine, the amounts and locations tested and approved for headache treatment are very different from that used for other indications.

With this protocol, developed and tested extensively, 31 small injections of 5 units each are placed at prescribed locations over the forehead, sides of the head, and back of the head and neck. The injections are just under the skin, creating a small bubble or wheal at the site that is usually not visible beyond a few hours

The PREEMPT injection protocol, i.e. injection of 155 U–195 U administered to 31 sites every 12-weeks as previously described, It has been argued that an injection paradigm customized to the individual patient would be preferable. However, we found no studies comparing the PREEMPT protocol with an alternative protocol

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

ATTACHED HEREWITH

8.0 LIST OF REFERENCES

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PROFORMA

Name: Sr. No

Age:

Sex:

MRD. No.

Address:

Occupation:

Chief complaints:

History of Headache:

- Onset :
- Duration :
- Frequency Pattern :
- Area involved

Associated symptoms:

- Triggers :
    1. Travelling
    2. Stress
    3. Sleep deprivation
    4. Fasting(missed meal)
    5. Weather change

- Relieving fector :
- Relieving Medication :
- Relapse :

Family History

1. Related to Headache :
2. Any other illness :

Past History

Hypertension:

Bronchial Asthma:

CVA:

DIABETES MELLITUS:

Personal History

1. Sleep Pattern :
2. Addiction History :
3. Diet History :
4. Allergy :
5. Any specific medication :
6. Exercise or any distressing activity :
7. Smoker/Non Smoker:
8. Alcoholic/Non-Alcoholic:
9. Other addiction:

Examination

GPE

Cyanosis:

Jaundice:

Oedema:

Pulse:

Blood Pressure:

Respiratory Rate:

Temperature:

Systemic Examination

Cardiovascular examination:

Respiratory examination:

Gastrointestinal examination:

Nervous system examination:

RADIO IMAGING

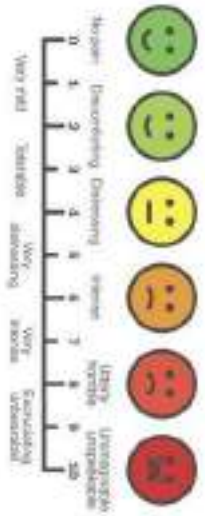
Dayanand Medical College & Hospital, Ludhiana
Department of Neurology

Name MRD No. Month Year

Date	Day	Headache Severity			Headache		Medication used (Acute)	Relief		Prophylactic medication
		0-4	4-7	7-10	>4hrs	<4hrs		YES	NO	

1. No. of hospital visit for headache this month_____

2. No. of days unable to work/function due to headache_____



Dr. Balveen 8799343480

INFORMED PATIENT CONSENT

Date: _____

I……..D/o, W/o, S/o…… ……am willing to participate in the study **"EVALUATION OF BOTULINUM TOXIN A AND GREATER OCCIPITAL NERVE BLOCK IN TREATMENT OF CHRONIC MIGRAINE"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

……. ……

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य "**Evaluation of Botulinum Toxin A and Greater Occipital Nerve block in treatment of chronic migraine**" में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

“Evaluation of Botulinum Toxin A and Greater Occipital Nerve block in treatment of chronic migraine” ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।
ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ